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THE WERNICKE SYNDROME

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In 1881 Wernicke,[1] on the basis of the cases of 3 patients studied carefully during life and at the autopsy table, delineated a clinical syndrome characterized by clouding of consciousness, varying ophthalmoplegias and ataxia. The author did not indict alcohol as the causative agent, but suggested that various toxins, including alcohol, might produce the clinicopathologic picture. Nonetheless, most subsequent cases of the syndrome were reported as occurring in inebriates, and alcoholism gradually came to be accepted as the etiologic basis of this condition. It is therefore important to emphasize that in Wernicke's original case the disease did not occur in an alcoholic person.

The patient in Wernicke's first case was a 20 year old seamstress who was admitted to the Charité after a suicidal attempt by the ingestion of sulfuric acid. She left the hospital in several days, but soon thereafter persistent and intractable vomiting set in, probably as the result of pyloric stenosis. The vomiting continued, and after one month she became stuporous and ophthalmoplegia and ataxia developed. In addition, there was moderate swelling of the optic disks with associated retinal hemorrhages. Her condition gradually grew worse, and she died one week after the onset of these complications. In his other 2 cases, however, the syndrome occurred in patients with chronic alcoholism who were admitted in delirium.

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1. Wernicke, C.: Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende, Berlin, T. Fischer, 1881, vol. 2, p. 229.

The essential pathologic changes were described by Wernicke[1] and have been further elaborated by others.[2] In general, the lesions are confined to the periventricular gray matter and are characterized by small foci of degeneration and varicose deformities of the blood vessels. There is subacute necrosis of the adjoining parenchyma, and small petechial hemorrhages are frequently, but not always, found throughout the lesions. The areas most constantly involved are the paramedian and the paraventricular nuclei of the thalamus and hypothalamus, the mamillary bodies, the periaqueductal region of the midbrain (nuclei of the third and fourth nerves), the abducens nucleus, the nucleus triangularis and nucleus Bechterew of the vestibular nerve and the dorsal nucleus of the vagus.

Jacobäus [3] reported a case of such a disease occurring in an alcohol addict, but observed that the polioencephalopathic changes were complicated by involvement of the spinal cord and peripheral nerves.

Bonhoeffer [4] stressed the fact that this condition was frequently associated with delirium tremens and the Korsakoff syndrome and pointed out that the pathologic picture is not that usually associated with inflammatory lesions.

Hunt [2a] reported an excellent clinical case and mentioned the pathologic observations in 22 others. He pointed out that the lesion was usually, but not invariably, confined to the gray matter and suggested that the condition in those cases in which the white matter was involved was closely related to the more usual type of inflammatory encephalitis. In addition, he spoke of the occasional involvement of the hindbrain and proposed the term polioencephalitis haemorrhagica inferior for such a condition.

Creutzfeld [5] confirmed the pathologic changes in 2 cases of Wernicke's disease, but noted in addition that cellular rarefaction and glial proliferation occurred in the cortex, more particularly in the frontal lobe.

Gamper's [2b] description of the pathologic anatomy can hardly be improved on. Interestingly, he associated the changes in the mamillary

2. (*a*) Hunt, J. R.: A Contribution to Our Knowledge of the Polioencephalitis Superior (Wernicke Type), New York M. J. **83**:289, 1906. (*b*) Gamper, E.: Zur Frage der Polioencephalitis hemorrhagica der chronischen Alkoholiker, Deutsche Ztschr. f. Nervenh. **102**:122, 1928. (*c*) Bender, L. and Schilder, P.: Encephalopathia Alcoholica (Polioencephalitic Haemorrhagica Superior of Wernicke), Arch. Neurol. & Psychiat. **29**:990 (May) 1933. (*d*) Alexander, L.: Wernicke's Disease, Am. J. Path. **16**:61, 1940.

3. Jacobäus, H.: Ueber einen Fall von Polioencephalitis hemorrhagica superior (Wernicke), Deutsche Ztschr. f. Nervenh. **5**:334, 1894.

4. Bonhoeffer, K.: Pathologisch-anatomische Untersuchungen an Alkoholdeliranten, Monatschr. f. Psychiat. u. Neurol. **5**:265, 1899.

5. Creutzfeld, R.: Hirnveränderungen bei Gerwohnheitstrinkern, Zentralbl. f. d. ges. Neurol. u. Psychiat. **50**:321, 1928.

bodies with the Korsakoff features which were so frequently observed as a complication.

Okhuma [6] suggested that alcohol was responsible only so far as it facilitated the production of some intermediary toxin, which in turn acted on the nervous system to produce the representative lesions and clinical symptoms. This concept was further elaborated by Neubürger,[7] who reported several cases occurring in nonalcoholic persons.

Bender and Schilder,[2c] in their excellent contribution, claimed that many atypical clinical pictures are seen and that one should not adhere too closely to Wernicke's original description. They indicated that the syndrome is frequently complicated by other types of alcoholic encephalopathy (delirium tremens, Korsakoff's syndrome, catatonic syndrome) and confirmed Jacobäus' observation that the spinal cord and peripheral nerves did not escape damage. In addition to the more usual lesions in the brain, they reported changes in the cortex and neocerebellum. Because the lesions were most marked in those portions of the nervous system adjacent to the cerebrospinal fluid, they, too, concluded, that a noxious agent carried in the spinal fluid was responsible. They mentioned, however, the possibility of vitamin deficiency and suggested that the cerebral changes might well be secondary to some generalized metabolic disease.

Brain [8] merely reaffirmed previous descriptions of the clinical pathology and apparently accepted alcohol as the etiologic agent.

In 1934 Prickett [9] described hemorrhagic lesions in the floor of the fourth ventricle in thiamine-deficient rats. He did not, however, investigate the underlying vascular disease and apparently did not recognize its similarity to the pathologic condition described by Wernicke.

Pappenheimer and Goettsch,[10] as a matter of fact, had previously described similar lesions in the cerebellum in chicks fed a vitamin E–deficient diet. The possibility of a thiamine deficiency was, however, not excluded.

Tanaka [11] reported an unusual case of the disease in a 5½ month, breast-fed infant. The mother had no definite signs of beriberi but was

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6. Okhuma, T.: Zur pathologischen Anatomie des chronischen Alkoholismus, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:94, 1930.

7. Neubürger, K.: Ueber Hirnveränderungen nach Alkoholmissbrauch, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:159, 1931.

8. Brain, R.: Diseases of the Nervous System, London, Oxford University Press, 1933.

9. Prickett, C. O.: The Effect of a Deficiency of Vitamin B_1 upon the Central and Peripheral Nervous Systems of the Rat, Am. J. Physiol. **107**:459, 1934.

10. Pappenheimer, A. M., and Goettsch, M.: A Cerebellar Disorder in Chicks, Apparently of Nutritional Origin, J. Exper. Med. **53**:11, 1931.

11. Tanaka, T.: So-Called Breast Milk Intoxication, Am. J. Dis. Child. **47**: 1286 (June) 1934.

pale, anemic and nephritic. He mentioned several cases of the disturbance in infants nursed by mothers with beriberi and stated that the symptoms were alleviated or cured when artificial feedings or a wetnurse was substituted for the mother's milk. The clinical picture and the brain after death in the reported cases were typical of the Wernicke syndrome.

In 1934 Laurette Bender [12] in another contribution reported involvement of the spinal cord in each of the 5 cases that she studied. (Her article contains an excellent bibliography, referring to similar observations by others.) Changes were most marked in the periventricular gray matter, the dorsal and lateral columns, the vegetative centers in the lateral horn and Clarke's column.

Wechsler [13] gave an excellent clinical description of the syndrome and reaffirmed its frequent association with delirium. He intimated that the ataxia might result from involvement of the brachium conjunctivum and the nucleus ruber, which were in such proximity to the usual site of pathologic involvement.

The following year Neubürger [14] reported 14 cases of the disturbance in nonalcoholic persons. Ten of these patients had malignant lesions of the gastrointestinal tract, and again the implication of an intermediary toxin was suggested. In the same year Bumke and Foerster [15] in their "Handbuch" mentioned the frequency with which delirium preceded this syndrome and remarked that when the disease did not end fatally the patient frequently was left with a residual Korsakoff syndrome.

In 1937 Neubürger [16] reported 3 additional cases of the syndrome in elderly women (nonalcoholic) with chronic atrophic gastritis in whom the condition developed as a terminal complication. He suggested that this condition would probably be encountered frequently if patients with carcinoma or cachexia were examined more carefully prior to death. He justly pointed out that since such persons are considered incurable, careful physical and neurologic examinations are not usually made when the patient lapses into a terminal stupor. In the same year Környey [17] published 2 similar cases occurring in nonalcoholic persons. One had a

12. Bender, L.: Myelopathia Alcoholica Associated with Encephalopathia Alcoholica, Arch. Neurol. & Psychiat. **31**:310 (Feb.) 1934.

13. Wechsler, I. S.: A Textbook of Neurology, ed. 3, Philadelphia, W. B. Saunders Company, 1935.

14. Neubürger, K.: Ueber die nichtalkoholische Wernickesche Krankheit, insbesondere über ihr Vorkommen beim Krebsleiden, Virchows Arch. f. path. Anat. **298**:68, 1936.

15. Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 828.

16. Neubürger, K.: Wernickesche Krankheit bei chronischer Gastritis, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**: 208, 1937.

17. Környey, K.: Wernicke-Korsakow-Process als Komplication bösartiger extraneuraler Geschwülste, Deutsche Ztschr. f. Nervenh. **144**:241, 1937.

malignant condition of the gastrointestinal tract and the other a carcinoma of the cervix. It is noteworthy that in both reports persistent vomiting characterized the disease picture prior to the development of encephalopathic signs. Wagener and Weir [18] reported that acute optic atrophy, hemorrhages in the retina, paralyses of the ocular muscles and nystagmus might all be caused by dietary or nutritional deficiency, and he commented on the frequency with which such complications followed persistent vomiting.

In 1938 the important contribution of Alexander and his coworkers [19] appeared. Their results may be summarized briefly as follows:

1. Wernicke's hemorrhagic polioencephalitis can be produced with significant regularity as a complication of beriberi in pigeons deprived of thiamine when large supplies of other vitamins (A, G [B_2] C and D) are fed.

2. If the pigeons are kept on an entirely vitamin-free diet, the resulting beriberi will only rarely be complicated by lesions of the Wernicke type.

3. Wernicke's disease cannot be produced in pigeons receiving crystalline thiamine hydrochloride, although they may be deprived of all other vitamins, or of any one other vitamin, for a period of over six months.

4. These observations suggested that thiamine possesses antiangiodegenerative, in addition to antineuritic, properties and that smaller amounts of thiamine are sufficient for its antiangiodegenerative than for its antineuritic action.

5. The administration of large doses of vitamins A, G [B_2] C or D in cases of thiamine deficiency probably raises the thiamine requirements of the tissues, and angiodegeneration manifests itself soon after the onset of neuronal degeneration.

After the appearance of this important paper, Zimmerman [20] reviewed some of his own pathologic material from thiamine-deficient pigeons and dogs and was able to confirm Alexander's work in every detail. Prickett, whose work has been previously cited,[9] came to a similar conclusion on reviewing his material from thiamine-deficient rats.

In the most recent edition of the textbook of Bing and Haymaker [21] the absence of inflammatory infiltration in the lesions is emphasized.

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18. Wagener, H. P., and Weir, J. F.: Ocular Lesions Associated with Post-Operative and Gestational Nutritional Deficiency, Am. J. Ophth. **20**:253, 1937.

19. Alexander, L.; Pijoan, M., and Myerson, A.: Beri-Beri and Scurvy, Tr. Am. Neurol. A. **64**:135, 1938.

20. Zimmerman, H. M.: The Pathology of the Nervous System in Vitamin Deficiencies, Yale J. Biol. & Med. **12**:23, 1939.

21. Bing, R., and Haymaker, W.: Textbook of Nervous Diseases, ed. 5, St. Louis, C. V. Mosby Company, 1940.

Moreover, the authors mention several personally observed cases of the syndrome in nondrinkers. Campbell and Biggart [22] reported 11 cases of the disease in nonalcoholic persons—all associated with gastrointestinal lesions or persistent vomiting. Only 3 of the patients had polyneuritis, but it must be stressed that the authors did not examine the patients personally. Ecker and Woltman [23] reported a case in which persistent vomiting followed cholecystectomy and intimated that Wernicke's disease might be a nutritional deficiency. They claimed that large doses of vitamin B complex and ascorbic acid effected a cure in some of their cases.

In 1940 Alexander [2d] amplified his original report and showed conclusively that the lesions of Wernicke's polioencephalitis occurring in man and the disease which he produced experimentally in thiamine-deficient pigeons were identical in their topographic distribution and in their morphologic and histologic characteristics. He also reported his pathologic observations on 16 patients, including 4 who were nonalcoholic (2 with associated scurvy, 1 with pernicious anemia and 1 with a marked depression leading to anorexia and cachexia).

A review of the literature to date therefore reveals the following essential points:

1. The clinical syndrome is not clearcut but in general consists of clouding of consciousness, varying ophthalmoplegias and ataxia. Furthermore, the syndrome is frequently preceded or accompanied by a delirious episode, and in those persons who recover a residual Korsakoff syndrome is frequently seen.

2. Pathologically, the lesions have been adequately described, but on occasions additional cortical and cerebellar changes have been noted. There is also reason to believe that the spinal cord and peripheral nerves do not escape. Moreover, the pathologic changes are not those usually associated with an inflammatory lesion.

3. Although the syndrome is most usually associated with chronic alcoholism, the evidence is fairly good that alcohol per se is not responsible for the clinical picture. Of the pathogenic factors which appear singly or in combination, a nutritional deficiency, more especially a deficiency of thiamine, seems to be the most obvious common factor. This assumption is further supported by the fact that a similar pathologic picture has been experimentally reproduced in thiamine-deficient animals (dogs, pigeons and rats).

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22. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy: Its Alcoholic and Non-Alcoholic Incidence, J. Path. & Bact. **48**:245, 1939.

23. Ecker, A. D., and Woltman, H. W.: Is Nutritional Deficiency the Basis of Wernicke's Disease? J. A. M. A. **112**:1794 (May 6) 1939.

With these facts in mind, we decided to review the cases of all patients with Wernicke's syndrome admitted to the medical service of the Bellevue Psychiatric Hospital from 1935 to 1940. They total 27 and are divided, for purposes of convenience, according to the mode of treatment.

REPORT OF CASES

Group I (table 1).—Treatment with a basal diet without added vitamins.

CASE 1.[24]—A man aged 56, alcoholic, entered the hospital in a confused, stuporous state. The pupils were small and fixed to light. In addition, he showed signs typical of nicotinic acid deficiency encephalopathy and peripheral neuropathy. With a basal diet, which was supplemented after twenty-four hours with 5 per cent dextrose in physiologic solution of sodium chloride,[24a] bilateral paralysis of the sixth nerve developed, and the patient died three days after admission.

This case illustrates the following points:

1. Presence of nicotinic acid deficiency encephalopathy on admission. This syndrome has recently been described by Jolliffe and his co-workers.[25] It is

TABLE 1.—*Basal Diet* Without Added Vitamins*

Case No., Age, Sex	History of Alcoholism	Mental Status on Admission	Neurologic Status on Admission	Treatment	Results of Treatment
1 56 yr. Male	Alcoholic	Confused; stuporous	Pupils small and fixed to light; nicotinic acid deficiency encephalopathy; peripheral neuropathy	Basal diet	Nicotinic acid deficiency encephalopathy and peripheral neuropathy were unchanged
				5% dextrose and physiologic solution of sodium chloride by vein and mouth	Bilateral paralysis of sixth nerve developed after one day; and patient died on the 3d day

* The basal diet contains 2,190 calories and represents a $\frac{\text{vitamin B}_1}{\text{calory}}$ ratio of 1.7, which is of borderline adequacy.

characterized by clouding of consciousness, changing cogwheel rigidities and uncontrollable sucking and grasping reflexes. The condition may occur independently or in association with pellagra, polyneuropathy, delirium tremens or the Wernicke syndrome or, in rare instances, with all four disorders. It is assumed that this syndrome represents a complete nicotinic acid deficiency, and treatment with nicotinic acid had resulted in a large percentage of cures in a condition that was previously invariably fatal.

2. Peripheral neuropathy on admission. This syndrome in the alcohol addict has been demonstrated by Jolliffe and his co-workers to be associated with a

24. Autopsy was done in this case. Gross changes characteristic of the Wernicke syndrome were observed in all. The brains are now being studied histologically and will be reported on subsequently.

24a. In this case, and in other cases in which it was given, 180 cc. of 5 per cent dextrose in physiologic solution of sodium chloride was given every hour by mouth.

25. Jolliffe, N.; Bowman, K. M.; Rosenblum, L. A., and Fein, H. D.: Nicotinic Acid Deficiency Encephalopathy, J. A. M. A. **114**:307 (Jan. 27) 1940.

deficiency of thiamine.[26] This vitamin, or more specially its diphosphoric ester, cocarboxylase, is necessary for the proper catabolism of pyruvic acid—one of the normal intermediary products of carbohydrate catabolism.[27] In the absence of thiamine, pyruvic acid accumulates in the body fluids and tissues. Utilizing the measurement of pyruvic acid as an indication of thiamine deficiency, Wortis and Bueding [28] were able to confirm the metabolic origin of peripheral neuropathy in alcohol addicts by showing that all such persons have an elevated pyruvate content of the blood and cerebrospinal fluid. They showed further that this metabolic upset can be completely reversed in certain instances by supplementing the patient's dietary with thiamine hydrochloride; in those cases in which thiamine hydrochloride therapy was not completely successful, it was suggested that irreversible pathologic changes had set in or that factors other than thiamine deficiency were contributing in some measure to the clinical picture.

3. Delay in development of ophthalmoplegia until peripheral neuropathy had already been well established and the thiamine requirements of the body further raised by the feeding of large quantities of carbohydrate, which necessitates, among other things, additional thiamine for its proper catabolism. This sequence of events will be noticed frequently in the cases to follow and not only suggests that the peripheral neuropathy and changes in the brain have a common origin but also confirms Alexander's contention that the changes in the peripheral nerves antedate the polioencephalopathic lesions.

4. Lack of response of the nicotinic acid deficiency encephalopathy and the peripheral neuropathy to the basal diet.

Group II (table 2).—Treatment with a basal diet plus nicotinic acid.

CASE 2.[24]—A man aged 39, alcoholic, was admitted in a confused, stuporous state with complete ophthalmoplegia and peripheral neuropathy. With the patient on a basal diet, the findings on admission did not change, and after two days acute nicotinic acid deficiency encephalopathy developed. Nicotinic acid was supplied in large amounts, but the patient died in twenty-four hours.

This case illustrates the following points:

1. Presence of peripheral neuropathy in a stuporous person with ophthalmoplegia. This combination will be found frequently in our cases.

2. Development of nicotinic acid deficiency encephalopathy in a patient fed a basal diet.

3. Lack of response of the acute nicotinic acid deficiency encephalopathy to treatment with nicotinic acid. Since the patient died almost immediately after therapy was instituted, it is assumed that either (*a*) irreversible metabolic or pathologic changes had set in or (*b*) factors other than nicotinic acid deficiency may, on occasion, produce a similar picture.

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26. Jolliffe, N., and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict, J. A. M. A. **107**:642 (Aug. 29) 1936. Goodhart, R., and Jolliffe, N.: Effects of Vitamin B (B_1) Therapy on the Polyneuritis of Alcohol Addicts, ibid. **110**:414 (Feb. 5) 1938.

27. Banga, I. L.; Ochoa, S., and Peters, R. A.: Pyruvate Oxidation in Brain: Active Form of Vitamin B_1 and Role of C_4 Dicarboxylic Acids, Biochem. J. **33**: 1109, 1939. Bueding, E., and Wortis, H.: Pyruvic Acid in the Blood and Cerebrospinal Fluid, Proc. Soc. Exper. Biol. & Med. **44**:245, 1940.

28. Wortis, H., and Bueding, E.: The Clinical Significance of Pyruvic Acid Content of the Blood and Cerebrospinal Fluid, Tr. Am. Neurol. A. **66**:90, 1940.

Group III (table 3).—Treatment with a regular ward diet without addition of vitamins.

CASE 3.—A man aged 30, alcoholic, entered the hospital with lobar pneumonia complicated by delirium. After a regular ward diet for two days nicotinic acid deficiency encephalopathy and complete ophthalmoplegia developed. At this point fluids high in vitamins were given, but the patient died within twenty-four hours.

This case illustrates the following point:

Development of acute nicotinic acid deficiency encephalopathy in a patient who was fed a seemingly adequate diet. This is probably related to the fact that the patient's metabolic requirements were greatly elevated by the presence of an infection (pneumonia) and delirium, with its marked increase in psychomotor activity. Under such circumstances, an ordinary ward diet is apparently insufficient to cover adequately the metabolic demands of the organism.[29]

CASE 4.—A woman aged 33, alcoholic, entered the hospital in an acute delirium, which cleared in three days with a ward basal diet and was replaced by a Korsakoff syndrome. The basal diet was continued, and two days later complete

TABLE 2.—*Basal Diet with Nicotinic Acid*

Case No., Age, Sex	History of Alcoholism	Mental Status on Admission	Neurologic Status on Admission	Treatment	Results of Treatment
2 39 yr., Male	Alcoholic	Confused; stuporous	Complete ophthalmoplegia; peripheral neuropathy	Basal diet	On 2d day nicotinic acid deficiency encephalopathy developed
				Nicotinic acid	Patient died within 24 hours; encephalopathy unimproved

ophthalmoplegia, peripheral neuropathy and ataxia developed. At this point, a regular ward diet (adequate in all the vitamins) was substituted for the basal diet, and nine days later the ophthalmoplegia had cleared completely. The Korsakoff syndrome, the peripheral neuropathy and the ataxia persisted.

This case illustrates the following points:

1. Clearing of alcoholic delirium with the patient on a ward basal diet. This is at variance with recent reports which have attempted to relate delirium tremens to a deficiency of thiamine or nicotinic acid.[30] Wortis [29] has already given his

29. Wortis, H.: Delirium Tremens, Quart. J. Stud. Alcohol **1**:251, 1940.

30. Kiene, H. E.; Streitweiser, R., and Miller, H. J.: Role of Vitamin B_1 in Delirium Tremens, J. A. M. A. **114**:2191 (June 1) 1940. Kloster, J.: B_1 Vitaminbehandlung bei Delirium tremens, Nervenarzt **11**:413, 1938. Stantesson, C. G.: Vitamin B_1 Therapy of Delirium Tremens, Svenska läk.-tidning **36**:926, 1939. Pagnies, P.: Anorexie mentale et hypophyse, Presse méd. **47**:668, 1939. Mainzer, F., and Krause, M.: Nicotinic Acid in Treatment of Delirium Tremens, Brit. M. J. **2**:331, 1939. May, A. M.: Use of Nicotinic Acid in Vitamin Deficiency Psychoses Associated with Alcoholism, M. Rec. **150**:124, 1939. Sydenstricker, V. P., and Cleckley, H. M.: The Effect of Nicotinic Acid in Stupor, Lethargy and Various Other Personality Disorders, read at the Ninety-Sixth Annual Meeting of the American Psychiatric Association, Cincinnati, May 22, 1940.

TABLE 3.—*Regular Ward Diet* Without Additional Vitamins*

Case No., Age, Sex	History of Alcoholism	Mental Status on Admission	Neurologic Status on Admission	Treatment	Results of Treatment
3 30 yr. Male	Alcoholic	Delirium accompanying pneumonia	Pupils equal and reacting sluggishly to light; neuropathy and cerebellar signs could not be evaluated because of patient's condition	Regular ward diet and fluids	On 2d day complete ophthalmoplegia and nicotinic acid deficiency encephalopathy developed
				High vitamin fluids †	Patient died within 24 hours; neurologic findings not changed before death
4 33 yr. Female	Alcoholic	Delirious	.....	Basal diet	After 3 days delirium cleared and was replaced by a Korsakoff syndrome; 2 days later complete ophthalmoplegia, peripheral neuropathy and ataxia developed
				Regular ward diet	After 9 days ophthalmoplegia cleared, but Korsakoff syndrome, peripheral neuropathy and ataxia remained
5 69 yr. Male	None; patient had not been eating	Confused; stuporous; clouding of consciousness	Complete ophthalmoplegia; irregular sluggish pupils; peripheral neuropathy	Regular ward diet	After 3 days ophthalmoplegia cleared, stupor was replaced by a Korsakoff syndrome and peripheral neuropathy remained unchanged
6 38 yr. Female	None; patient had active pulmonary tuberculosis; vomiting for 2 weeks	Confused	Complete ophthalmoplegia; irregular, fixed pupils; peripheral neuropathy	Regular ward diet	Nicotinic acid deficiency encephalopathy and stomatitis developed after 2 days; course continually downhill, and patient died 15 days after admission; mental and neurologic pictures were unchanged
7 38 yr. Male	Alcoholic	Delirious	Complete ophthalmoplegia; peripheral neuropathy	Regular ward diet	Ophthalmoplegia was unimproved, and peripheral neuropathy grew worse; nicotinic acid deficiency encephalopathy developed and patient died in 4 days
8 59 yr. Female	Alcoholic	Delirious	Complete ophthalmoplegia; ataxia; peripheral neuropathy	Regular ward diet	After 3 days delirium cleared and was replaced by a Korsakoff syndrome; ophthalmoplegia cleared in 6 days; neuropathy unchanged
9 43 yr. Female	Alcoholic	Delirious	Bilateral paralysis of 6th nerve; peripheral neuropathy	Regular ward diet	Patient became stuporous, and the nicotinic acid deficiency stomatitis present on admission grew worse; after 24 hours nicotinic acid was added to diet, without apparent effect on the mental or neurologic picture; on 3d day in hospital patient went into peripheral circulatory collapse and died

* The regular ward diet contains about 2,500 calories, with a vitamin B_1 = calory ratio of 3.3.

† These fluids—orange juice, tomato juice, milk and eggnog—were given alternately each hour in amounts of 180 cc.

reasons for believing that a deficiency of thiamine or nicotinic acid is not specific in the causation of delirium tremens and that administration of these vitamins in the treatment of the disease is nonspecific. They are, however, invaluable in the treatment of certain other syndromes (peripheral neuropathy, Wernicke's syndrome and acute nicotinic acid deficiency encephalopathy) which frequently accompany or complicate the delirious episode. Delirium tremens may of course be related to a deficiency in some as yet undiscovered or untried vitamin, but the evidence for thiamine and nicotinic acid is meager indeed. It is possible, however, that these vitamins help in nonspecific fashion by augumenting oxidation in the brain. It is now known that thiamine (or more specifically its diphosphoric ester, cocarboxylase) is concerned in the proper catabolism of carbohydrate at the pyruvic acid stage. Nicotinic acid is a known vasodilator and may increase cerebral functioning by facilitating the cerebral blood flow. It should therefore be made clear that while one usually gives delirious patients adequate amounts of thiamine hydrochloride and nicotinic acid, this is done with the idea of preventing complications.[31]

2. Development of ophthalmoplegia, peripheral neuropathy and ataxia following a delirious episode.

3. Response of the ophthalmoplegia to a regular ward diet, although the rest of the neuropsychiatric picture was relatively unaffected. This, again, would seem to confirm Alexander's suggestion that smaller amounts of thiamine are necessary to prevent ophthalmoplegia (angiodegeneration in the region of the nuclei of the eye muscles) than are needed to avoid neuritic symptoms. It should also be noted that the delirium had subsided at this point and the patient's metabolic requirements had thereby been markedly lowered.

CASE 5.—A man aged 69 entered the hospital in a confused, stuporous state, with marked clouding of consciousness. In addition, he showed irregular, sluggish pupils, complete ophthalmoplegia and peripheral neuropathy. He was nonalcoholic but had been markedly depressed after the death of his wife, one month prior to admission. He had locked himself in his room and refused to eat. The neighbors finally called the police and insisted on his removal to the hospital. With a regular ward diet, the ophthalmoplegia cleared in three days, the stupor was replaced by a Korsakoff syndrome and the peripheral neuropathy was unchanged.

This case illustrates the following points:

1. Occurrence of Wernicke's syndrome in a nonalcoholic person who had not been eating properly.

2. The fairly prompt response of the stupor and the ophthalmoplegia to an adequate diet.

CASE 6.—A woman aged 38, nonalcoholic, entered the hospital with active pulmonary tuberculosis and a history of persistent vomiting for two weeks prior to admission. On admission she was confused; the pupils were irregular and fixed, and complete ophthalmoplegia and peripheral neuropathy were present. With a regular ward diet, an acute nicotinic acid deficiency encephalopathy was superimposed on the picture at admission, the patient's condition became gradually worse and she died in fifteen days.

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31. Bowman, K. M.; Wortis, H., and Keiser, S.: The Treatment of Delirium Tremens, J. A. M. A. **112**:1217 (April 1) 1939.

This case illustrates the following points:

1. Occurrence of Wernicke's syndrome in a nonalcoholic person who had a severe infection (which in itself raised her metabolic needs) and who had further depleted her nutrition by persisent vomiting for two weeks prior to admission.

2. Inadequacy of a regular ward diet in the presence of a severe infection. Not only did an additional nutritional encephalopathy (acute nicotinic acid deficiency encephalopathy) develop while the patient was under observation, but the ophthalmoplegia and the peripheral neuropathy showed no improvement prior to her death.

CASE 7.—A man aged 38, alcoholic, entered the hospital in delirium, with complete ophthalmoplegia and peripheral neuropathy. With a regular ward diet, the peripheral neuropathy grew worse and the ophthalmoplegia was unchanged. On the fourth day acute nicotinic acid deficiency encephalopathy developed, and the patient died within twenty-four hours.

This case illustrates the following point: Inadequacy of a regular ward diet to prevent or cure certain complicating factors (ophthalmoplegia, Wernicke's syndrome, acute nicotinic acid deficiency encephalopathy) when a patient is in active delirium.

CASE 8.—A woman aged 59, alcoholic, entered the hospital in delirium, with complete ophthalmoplegia, ataxia and peripheral neuropathy. With a regular ward diet, the delirium cleared and was replaced by a Korsakoff syndrome. The ophthalmoplegia, which had shown only slight improvement up to this point, now improved markedly and cleared completely three days after the delirium subsided. The peripheral neuropathy was unchanged.

This case illustates the following points:

1. Subsidence of a delirious episode treated with a regular ward diet (adequate in vitamins) without vitamin supplements.

2. Prompt response of the ophthalmoplegia when the delirium subsided and the metabolic needs of the patient were decreased. At this point the thiamine in the diet was apparently sufficient to reverse the ophthalmoplegia.

3. Lack of response of the peripheral neuropathy to amounts of thiamine sufficient to reverse the ophthalmoplegia.

CASE 9.—A woman aged 43, alcoholic, entered the hospital in delirium, complicated by bilateral paralysis of the sixth nerve, peripheral neuropathy and nicotinic acid deficiency stomatitis. The patient was given a regular diet but became markedly stuporous. After twenty-four hours nicotinic acid was added to the diet, with no apparent effect. On the third day of hospitalization the patient went into peripheral circulatory collapse (thiamine deficiency?). Thiamine hydrochloride was given intravenously, but the patient was already in extremis and died soon after.

This case illustrates the following points:

1. Lack of response of the ophthalmoplegia to a regular ward diet and nicotinic acid in a delirious patient.

2. Lack of response of the stupor to nicotinic acid.

Group IV (table 4).—Treatment with a high vitamin diet plus vegex.

CASE 10.—A man aged 38, alcoholic, entered the hospital in a stuporous confused state, with unequal pupils, bilateral paralysis of the sixth nerve, dysarthria and peripheral neuropathy. With a basal diet, the clinical picture on admission

TABLE 4.—*High Vitamin Diet with Added Vegex**

Case No., Age, Sex	History of Alcoholism	Mental Status on Admission	Neurologic Status on Admission	Treatment	Results of Treatment
10 38 yr. Male	Alcoholic	Stuporous; confused	Bilateral paralysis of 6th nerve; unequal pupils; peripheral neuropathy; dysarthria	Basal diet	Nicotinic acid deficiency encephalopathy developed
				High vitamin and calory diet plus parenteral administration of liver extract daily	Stupor and ophthalmoplegia cleared in 3 days; encephalopathic manifestations cleared in 7 days, leaving a Korsakoff syndrome, which, with the peripheral neuropathy, cleared markedly in 3 weeks
11 50 yr. Female	Alcoholic	Delirious	Complete ophthalmoplegia; sluggish pupils; peripheral neuropathy	Basal diet	Nicotinic acid deficiency stomatitis and dermatitis present on admission grew worse and was complicated by encephalopathy on 2d day
				Vegex, parenteral injections of liver extract and cod liver oil added	Ophthalmoplegia, stomatitis, dermatitis and encephalopathy cleared after 9 days, but erysipelas developed and patient died 21 days later
12 45 yr. Female	Alcoholic	Confused; stuporous	Bilateral paralysis of 6th nerve; irregular, fixed pupils; peripheral neuropathy; dysarthria	Regular ward diet	On the 3d day nicotinic acid deficiency stomatitis and encephalopathy developed
				High vitamin B diet, vegex, and parenteral injections of liver extract	Encephalopathy and stomatitis improved, and lateral motion of eyeballs appeared after 2 days; improvement continued until bronchopneumonia developed; patient died on 12th day
13 51 yr. Male	Alcoholic	Confabulatory delirium	Complete ophthalmoplegia; ataxia; peripheral neuropathy	Fluids, solution of dextrose and isodium chloride by mouth	After 4 days central blindness developed, the original status remaining unchanged
				Fluids high in vitamins, vegex, nicotinic acid	After 9 days condition remained unimproved
				Pyridoxine †	Patient became stuporous and progressively worse and died after 26 days, without change
14 38 yr. Male	Alcoholic	Confused	Peripheral neuropathy	Basal diet	After 3 days stomatitis and glossitis presented on admission grew worse, and patient went into a confabulatory delirium, which was followed by dissociation of movements of eyeballs and bilateral paralysis of 6th nerve
				Pyridoxine, nicotinic acid	No improvement; marked clouding, stupor, ataxia and increased severe peripheral neuropathy developed
				High vitamin B diet, vegex	Patient died 9 hours after institution of this therapy (6 days after admission)

* About 18 Gm. of vegex per day was given, an amount which contains about 200 international units of vitamin B_1.

† Pyridoxine hydrochloride was given intramuscularly or intravenously in amounts of 100 mg. daily.

was complicated by the development of acute nicotinic acid deficiency encephalopathy. The patient was then placed on a high vitamin, high calory diet plus intramuscular injections of liver extract. The stupor and ophthalmoplegia cleared in three days. The sucking and grasping reflexes disappeared in seven days, leaving the patient with a residual Korsakoff syndrome. Both this and his peripheral neuropathy improved markedly under continuation of the same regimen for three weeks.

This case illustrates the following points:

1. Inadequacy of borderline diets for alcoholic patients and the frequency with which clinical complications appear (acute nicotinic acid deficiency encephalopathy).

2. Clearing of the ophthalmoplegia and the nicotinic acid deficiency encephalopathy on a high vitamin, high calory diet with intramuscular injections of liver extract (which contains large amounts of thiamine and nicotinic acid).

3. The eventual clearing of the Korsakoff syndrome and the peripheral neuropathy with the same diet. Recently, it has been suggested that thiamine deficiency may be the cause of the Korsakoff psychosis.[32] These reports are probably the result of premature optimism. The confabulatory features of an acute delirium frequently clear up on a thiamine-deficient diet.[33] In cases of chronic Korsakoff psychosis, Bowman and his co-workers [34] have shown that thiamine hydrochloride appears to be of help in recovery, but is in no wise specific.

4. The response of peripheral neuropathy in the alcohol addict to a diet high in vitamins, particularly thiamine.

CASE 11.[24]—A woman aged 50, alcoholic, entered the hospital in delirium, with sluggish pupillary responses, complete ophthalmoplegia and peripheral neuropathy. Her condition was further complicated by the presence of nicotinic acid deficiency stomatitis and dermatitis. She was given a basal diet, with no change in her condition except for the development of nicotinic acid deficiency encephalopathy. At th s point the diet was supplemented with vegex, cod liver oil and liver extract, administered parenterally. The stomatitis, dermatitis and ophthalmoplegia responded in nine days, but erysipelas developed and the patient died two days later.

This case illustrates the following points:

1. Therapeutic response of the pellagrous lesions and the ophthalmoplegia to a diet containing ample nicotinic acid and vitamin B_1 (contained in the vegex and liver extract).

2. Clearing of the ophthalmoplegia, despite the fact that the patient died of an intercurrent infection.

CASE 12.—A woman aged 45, alcoholic, entered the hospital in a confused, stuporous condition, with irregular, fixed pupils, bilateral paralysis of the sixth nerve, dysarthria and peripheral neuropathy. After a regular ward diet for three days, nicotinic acid deficiency stomatitis and encephalopathy developed. At

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32. Weiss, S., in Cecil, R. L.: Textbook of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1938, p. 562. Brodsky, M.: Treatment of Alcoholic Psychoses with Thiamin Chloride, J. Connecticut M. Soc. **2**:228, 1938.

33. Wortis, H.: Vitamins in Nervous Health and Disease, New York State J. Med. **39**:1178, 1939.

34. Bowman, K. M.; Goodhart, R. S., and Jolliffe, N.: The Korsakoff Syndrome, J. Nerv. & Ment. Dis. **90**: 569, 1939.

this point a high vitamin B diet plus vegex and liver extract, administered parenterally, was substituted for the regular diet. The encephalopathy and stomatitis improved markedly, and lateral movements of the eyeballs were now apparently normal (cooperation was poor). Unfortunately, bronchopneumonia developed, and the patient died twelve days later.

This case illustrates the following points:

1. Frequent inadequacy of the regular ward diet in cases of alcoholic avitaminosis. Furthermore, one is dependent on the cooperation of the nurses and the patient to insure eating of the food which is offered, a condition not always possible with uncooperative psychotic patients.

2. Response of the ophthalmoplegia and the nicotinic acid deficiency stomatitis and encephalopathy to thiamine and nicotinic acid (contained in the high vitamin B diet, the vegex and the liver extract).

CASE 13.—A man aged 51, alcoholic, entered the hospital in a confabulatory delirium, with complete ophthalmoplegia, ataxia and peripheral neuropathy. He was given fluids, physiologic solution of sodium chloride and 5 per cent dextrose, with no change in his condition after four days except inability to see. Examination of the fundi revealed nothing abnormal. He was given fluids high in vitamins, vegex and nicotinic acid, with no change in his mental status or ophthalmoplegia. After five days this dietary was supplemented with pyridoxine hydrochloride; but the patient's condition became worse, and he died twenty-six days later, with the ophthalmoplegia still complete.

This case illustrates the following points:

1. Lack of response of the ophthalmoplegia to thiamine. We know of no explanation for this, since the thiamine was apparently given soon enough (the patient did not die until twenty-two days later). It may be that since the vitamin was given orally, proper absorption and utilization did not take place. Furthermore, it is conceivable that in certain persons the ability to phosphorylate thiamine to its active form, cocarboxylase, is defective.

CASE 14.[24]—A man aged 38, alcoholic, entered the hospital in a confused state, with peripheral neuropathy and nicotinic acid deficiency stomatitis and glossitis. The family volunteered the information that the patient had been suffering from diarrhea for one month prior to admission. After three days on a basal diet, the patient went into a confabulatory delirium, which was followed the next day by dissociation of movements of the eyeballs and bilateral paralysis of the sixth nerve. At this point the diet was supplemented with pyridoxine hydrochloride and nicotinic acid; but the patient grew more stuporous, his peripheral neuropathy grew worse and he became markedly ataxic. Vegex and a high vitamin B diet were now given, but the patient died within nine hours after the institution of this regimen.

This case illustrates the following:

1. Development of ophthalmoplegia in a person who was already definitely deficient in thiamine (peripheral neuropathy) following a delirious episode.

2. Lack of response of the stupor or ophthalmoplegia to nicotinic acid or pyridoxine.

3. Failure of thiamine to reverse the ophthalmoplegia, which in this case was probably related to the time at which it was given. It is more than likely that irreversible metabolic and pathologic changes had already set in. As a matter of fact, the patient died less than nine hours after this regimen was instituted.

Group V (table 5).—Treatment with a basal diet plus thiamine hydrochloride.

CASE 15.—A man aged 38, alcoholic, entered the hospital in a stuporous condition. Physical examination revealed bilateral paralysis of the sixth nerve, ataxia and peripheral neuropathy. The patient was given a basal diet and thiamine hydrochloride. The stupor and ophthalmoplegia were markedly improved in one day and had completely disappeared on the third day of this regimen. A Korsakoff picture then took the foreground and persisted until the patient's discharge, twenty-eight days later. The peripheral neuropathy, incidentally, cleared on the sixteenth day of the regimen.

This case illustrates the following points:

1. Prompt response of the ophthalmoplegia to thiamine hydrochloride.

2. Clearing of the stupor with thiamine hydrochloride therapy. This is likely not a specific effect. The functioning of the brain is dependent on a carbohydrate substrate and an adequate supply of oxygen. In addition, various enzyme and coenzyme systems are necessary for the proper breakdown and utilization of this carbohydrate. Among the more important of the latter systems is cocarboxylase (the diphosphoric ester of thiamine). Experiments have shown conclusively that in the thiamine-deficient subject there is a diminished oxygen uptake of the brain, which is restored to normal when this dietary deficiency is corrected.[35] This has been confirmed by the recent in vivo experiments of Himwich and his associates on patients with beriberi.[36] Similarly, nicotinic acid has been described as useful in arousing persons from stuporous states,[37] but the exact mechanism of this action is not yet known. The importance of vitamins in metabolism of brain tissue has been firmly established, and a specific neuropsychiatric syndrome related to complete deficiency in nicotinic acid has been described.[25] It is likely that as knowledge increases many similar syndromes will be described, but such a correlation is not possible at present. Furthermore, it may be that these deficiency states interfere with brain metabolism in such a way as to produce some common disturbance like anoxia and that this in turn produces the observable clinical picture.

3. Therapeutic response of the peripheral neuropathy to thiamine hydrochloride.

4. Persistence of the Korsakoff syndrome even after prolonged treatment with thiamine hydrochloride.

CASE 16.—A man aged 61, who was chronically alcoholic, entered the hospital in a confabulatory delirium, with peripheral neuropathy and ataxia. After a ward basal diet for two days there developed bilateral paralysis of the sixth nerve, which progressed to total ophthalmoplegia two days later. When thiamine hydrochloride (given parenterally) was added to the patient's diet, the ophthalmoplegia improved markedly in twenty-four hours, and movements of the eye muscles were entirely normal within forty-eight hours. The peripheral neuropathy improved

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35. Peters, R. A.: The Biochemical Lesion in Vitamin B_1 Deficiency, Lancet **1**:1161, 1936.

36. Himwich, H. E.; Spies, T. D.; Fazekas, J. F., and Nesin, S.: Cerebral Carbohydrate Metabolism During Deficiency of Various Members of the Vitamin B Complex, Am. J. M. Sc. **199**:849, 1940.

37. Cleckley, H. M.; Sydenstricker, V. P., and Geeslin, L. E.: Nicotinic Acid in the Treatment of Atypcial Psychotic States, J. A. M. A. **112**:2107 (May 27) 1939.

TABLE 5.—*Basal Diet Plus Thiamine Hydrochloride* *

Case No., Age, Sex	History of Alcoholism	Mental Status on Admission	Neurologic Status on Admission	Treatment	Results of Treatment
15 38 yr. Male	Alcoholic	Stuporous	Bilateral paralysis of 6th nerve; ataxia; peripheral neuropathy	Basal diet plus thiamine hydrochloride	After 1 day, stupor and ophthalmoplegia were improved, the latter being completely cured in 3 days; Korsakoff picture remained until discharge, 28 days later; peripheral neuropathy cleared after 16 days
16 61 yr. Male	Alcoholic	Confabulatory delirium	Peripheral neuropathy; ataxia	Basal diet	After 2 days bilateral paralysis of 6th nerve developed, which progressed to complete ophthalmoplegia 2 days later
				Thiamine hydrochloride	Ophthalmoplegia improved markedly in 1 day and cleared in 2 days; peripheral neuropathy improved markedly, but the patient was left with a residual Korsakoff syndrome
17 35 yr. Male	Alcoholic	Delirious	Bilateral paralysis of 6th nerve; peripheral neuropathy	Basal diet, solution of dextrose and sodium chloride	Condition remained unchanged; evidence of severe toxic hepatitis
				Thiamine hydrochloride	Patient grew more stuporous and died on 2d day; hepatic insufficiency
18 48 yr. Female	Alcoholic	Confabulatory delirium	Peripheral neuropathy	Basal diet plus solution of dextrose and sodium chloride	After 2 days patient became more stuporous and ataxic, and bilateral paralysis of 6th nerve and nicotinic acid deficiency stomatitis developed
				Nicotinic acid †	Pellagrous manifestations improved, but ophthalmoplegia remained
				Thiamine hydrochloride	After 2 days marked increase in the lateral motion of eyeballs, but bronchopneumonia developed and patient died on 7th day
19 39 yr. Female	Alcoholic	Confabulatory delirium	Complete ophthalmoplegia; peripheral neuropathy-ataxia	Basal diet	After 2 days delirium cleared and was replaced by a Korsakoff syndrome; ocular findings were unchanged
				Thiamine hydrochloride	After 2 days ophthalmoplegia cleared; the peripheral neuropathy showed gradual improvement, but the Korsakoff picture remained
20 38 yr. Male	Alcoholic	Delirious	Bilateral paralysis of 6th nerve; ataxia; peripheral neuropathy	Goldberger diet	Stomatitis present on admission grew worse
				Liver residue	Stomatitis cleared in 2 days; ocular condition remained the same
				Thiamine hydrochloride	After 2 days ophthalmoplegia cleared; after 4 days delirium cleared; Korsakoff syndrome and peripheral neuropathy became chronic and were present 1 month later, along with ataxia and a cerebellar syndrome

* From 100 to 200 mg. of thiamine hydrochloride per day was given intramuscularly or intravenously.

† Doses of nicotinic acid were from 500 to 1,000 mg. per day.

markedly, but, again, the patient was left with a residual Korsakoff syndrome. Of importance in this case are the following points:

1. Prompt response of the ophthalmoplegia to thiamine hydrochloride.

2. Persistent Korsakoff syndrome despite thiamine therapy.

3. Persistent ataxia. Ataxia in cases of this disease is difficult to evaluate in that it may be related to involvement of the peripheral nerve, the spinal cord, the spinocerebellar tract, the cerebellum, the extracellular nuclei or possibly even the frontal lobe. In view of the work of Pappenheimer and Goettsch,[10] in which they were able to produce a hemorrhagic cerebellar lesion in chicks fed a diet deficient in vitamin E, this vitamin deserves a trial.

Case 17.—A man aged 35, alcoholic, entered the hospital in delirium, with bilateral paralysis of the sixth nerve, peripheral neuropathy and toxic hepatitis. With a basal diet plus 5 per cent dextrose in physiologic solution of sodium chloride, no particular change in the clinical picture occurred except that he became more stuporous. Thiamine hydrochloride was then given parenterally, but the patient died of hepatic insufficiency.

This case illustrates the following points:

Lack of response to thiamine hydrochloride of the stupor and ophthalmoplegia in a person with toxic hepatitis. The importance of the liver in various enzyme activities and the utilization of vitamins is just beginning to be understood. It is possible that the coma into which patients with hepatic insufficiency sink prior to death represents a metabolic encephalopathy conditioned by a damaged liver. To what extent the diseased liver interferes with carbohydrate metabolism and enzyme activities on which the brain is dependent for its normal functioning is a subject for future investigation.

Case 18.—A woman aged 49, alcoholic, entered the hospital in a confabulatory delirium. She showed, in addition, evidence of peripheral neuropathy. On a basal diet plus dextrose in physiologic solution of sodium chloride, she became more stuporous and ataxic, and bilateral paralysis of the sixth nerve developed. Later, a nicotinic acid deficiency stomatitis became apparent. The reasons for the development of these complications in delirious persons have already been discussed in connection with the preceding cases. Two days later, after nicotinic acid was added to the patient's dietary, the following changes were noted: (1) the nicotinic acid deficiency stomatitis cleared up; (2) the patient grew clearer mentally; (3) the ophthalmoplegia, however, was unchanged. At this point thiamine hydrochloride was added, and the ophthalmoplegia disappeared in two days. Unfortunately, bilateral bronchopneumonia developed and the patient died.

This case illustrates the following points:

1. Lack of response of the ophthalmoplegia to nicotinic acid and its prompt and dramatic response to thiamine hydrochloride.

2. Apparent improvement in the patient's mental torpor with nicotinic acid. In case 15 we reported a similar result with thiamine hydrochloride. Such observations emphasize the dangers of uncontrolled observations in this field.

Case 19.—A woman aged 39, who was chronically alcoholic, entered the hospital in a confabulatory delirium. This was complicated by the presence of complete ophthalmoplegia and peripheral neuropathy. With the patient on the ward basal diet, the delirium cleared on the second day and was replaced by a Korsakoff syndrome. The ophthalmoplegia was unaffected. The patient could

now cooperate sufficiently so that ataxia was apparent on walking and in tests of coordination. At this point, thiamine hydrochloride was added, and the ophthalmoplegia cleared in two days, but the patient was left with a residual Korsakoff syndrome. The peripheral neuropathy showed marked improvement, but was not entirely cured.

This case illustrates the following points:

1. Clearing of the delirium on a diet which contained no appreciable amount of thiamine or nicotinic acid.

2. Prompt response of the ophthalmoplegia to thiamine hydrochloride.

3. Lack of return to normal functioning of the peripheral nerves in an alcoholic patient fed a basal diet supplemented with thiamine hydrochloride alone. This, again, suggests that irreversible pathologic changes have set in or that factors other than thiamine deficiency are responsible in some measure for the clinical neuropathy. Many patients with so-called irreversible peripheral neuropathy show continued improvement when a diet rich in other nutritional factors is added to the thiamine therapy. Knowledge of normal nerve metabolism is by no means complete; as additional light is shed on other factors, it may be that certain irreversible neurologic conditions will prove to be completely reversible. Zimmerman[20] has already suggested that riboflavin may be responsible for some of the demyelination seen in the peripheral nerves, but this experimental observation still requires clinical confirmation.

Case 20.—A man aged 38, alcoholic, entered the hospital in delirium, complicated by bilateral paralysis of the sixth nerve, ataxia and peripheral neuropathy. There was also evidence of nicotinic acid deficiency stomatitis. The patient was given a Goldberger diet, with no essential change in his condition. With liver residue,[37a] the stomatitis cleared in two days, but the delirium, ophthalmoplegia and ataxia remained unchanged. At this point thiamine hydrochloride was added to the diet, with the following results: (1) The ophthalmoplegia cleared in two days; (2) delirium cleared in four days and was replaced by a Korsakoff syndrome; (3) the peripheral neuropathy showed marked improvement, but there was still not a complete return to normal functioning of the peripheral nerves.

This case illustrates the following points:

1. Clearing of the nicotinic acid deficiency stomatitis with liver residue.

2. Persistence of the delirious episode with administration of liver residue (nicotinic acid). This confirms the work of Spies and associates,[38] Rosenbaum and associates[39] and Wortis,[29] who noted no essential difference in their results when thiamine hydrochloride and nicotinic acid were given or were omitted in the routine therapy of alcoholic delirium. As a matter of fact, Rosenbaum and associates reported the experimental production of an attack of delirium tremens in a patient with chronic alcoholism who was given huge doses of thiamine

37a. Liver residue is an alcoholic precipitate of an aqueous extract of liver (Ruffin, J. M., and Smith, D. T.: South. M. J. **30**:4 [Jan.] 1937).

38. Spies, T. D.; Aring, C. D.; Gelpern, J., and Bean, W. B.: Mental Symptoms of Pellagra and Their Relief with Nicotinic Acid, Am. J. M. Sc. **196**:461 (Oct.) 1938.

39. Rosenbaum, M.; Piker, P., and Lederer, H.: Delirium Tremens: A Study of Various Methods of Treatment, read at the Ninety-Sixth Annual Meeting of the American Psychiatric Association, Cincinnati, Ohio, May 23, 1940.

hydrochloride and nicotinic acid but was allowed to drink about a quart (1,000 cc.) of whisky per day. The delirium started thirteen days after this regimen was instituted.

3. Prompt response of the ophthalmoplegia to thiamine hydrochloride.

4. Improvement of the peripheral neuropathy with thiamine hydrochloride.

5. Persistence of the ataxia with a diet adequate in vitamin B_1 and nicotinic acid, suggesting that if this portion of the syndrome is related to a nutritional deficiency, it is of some factor other than thiamine or nicotinic acid. It is, of course, also possible that the cerebellum, because of its high respiratory rate,[40] is extremely sensitive to lack of oxygen and that irreversible changes may set in early. This is at least partially refuted by our observation on a patient with a so-called alcoholic cerebellar syndrome who has shown definite improvement during six months' treatment with a high vitamin, high calory diet, supplemented with thiamine hydrochloride, nicotinic acid and vitamin E.

Group VI (table 6).—Treatment with a regular diet plus thiamine hydrochloride.

Case 21.—A man aged 34, alcoholic, entered the hospital in a confabulatory delirium, complicated by sluggish pupillary responses, bilateral paralysis of the sixth nerve, ataxia and peripheral neuropathy. With a regular ward diet, the delirium cleared in four days, leaving the patient with a residual Korsakoff syndrome. The ophthalmoplegia was essentially unchanged, although certain examiners stated that there was some return of lateral movement of the eyeballs. Six days after admission thiamine hydrochloride was added to the dietary, and the ophthalmoplegia promptly cleared in two days. The ataxia, however, persisted.

This case illustrates the following points:

1. Frequent lack of response of the ophthalmoplegia to a regular ward diet, until thiamine hydrochloride is added in significant doses.

2. Persistence of the Korsakoff syndrome despite adequate thiamine therapy.

3. Persistence of ataxia, although a regular diet and adequate thiamine hydrochloride were supplied.

Case 22.—A woman aged 45, alcoholic, entered the hospital in a dull, confused state. There was a history of having passed through a delirious episode at home, prior to her admission to the hospital. On admission she showed pupillary inequality, complete ophthalmoplegia and peripheral neuropathy. There was further evidence of nutritional deficiency in the presence of nicotinic acid deficiency stomatitis and dermatitis. These nutritional deficiencies were undoubtedly contributed to by the diarrhea that was present on admission. How long this had existed prior to hospitalization could not be determined. She was given a Goldberger diet, with no apparent change except that her pellagrous manifestations grew more severe. Two days later nicotinic acid was added. The pellagrous manifestations grew less marked; the patient became much clearer mentally but the ophthalmoplegia remained unchanged. At this point, a regular diet supplemented with vegex was given, and she became even clearer mentally, but the ophthalmoplegia persisted unchanged for the six days that this diet was employed. At this point thiamine hydrochloride was added. The ophthalmoplegia improved greatly in one day and was entirely gone three days later. The peripheral

40. Dixon, T. F., and Meyer, A.: Respiration of Brain, Biochem. J. **30**:1577, 1936.

neuropathy also improved markedly, but the patient was left with a residual Korsakoff syndrome.

This case illustrates the following points:

1. Frequent improvement of mental status of dull, stuporous patients treated with nicotinic acid or thiamine hydrochloride.

2. Lack of response of the ophthalmoplegia to nicotinic acid and its prompt response when thiamine hydrochloride is added to the diet.

3. Residual Korsakoff syndrome despite thiamine therapy.

4. Frequency with which this sequence of events is initiated by a delirious episode.

5. Improvement of the peripheral neuropathy with thiamine therapy.

TABLE 6.—*Regular Diet with Added Thiamine Hydrochloride*

Case No., Age, Sex	History of Alcoholism	Mental Status on Admission	Neurologic Status on Admission	Treatment	Results of Treatment
21 34 yr. Male	Alcoholic	Confabulatory delirium	Bilateral paralysis of 6th nerve; sluggish pupils; ataxia; peripheral neuropathy	Regular ward diet	After 4 days delirium cleared, giving way to a Korsakoff syndrome; no definite improvement in ophthalmoplegia
				Thiamine hydrochloride	After 2 days ophthalmoplegia cleared, though nystagmus and ataxia remained
22 45 yr. Female	Alcoholic	Dull; confused (history of delirium before admission)	Complete ophthalmoplegia; pupils unequal and sluggish; peripheral neuropathy	Goldberger diet	The stomatitis, dermatitis and diarrhea present on admission grew worse; neurologic findings remained unchanged
				Nicotinic acid	Pellagrous manifestations improved, and patient clearer mentally
				Regular ward diet, vegex	Further mental clearing, but ophthalmoplegia remained the same after 6 days
				Thiamine hydrochloride	Ophthalmoplegia improved in 1 day and cleared entirely in 3 days; peripheral neuropathy and Korsakoff picture improved

Group VII (table 7).—Treatment with high vitamin diet with added thiamine hydrochloride.

CASE 23.—A man aged 52, alcoholic, entered the hospital in a confabulatory delirium, complicated by bilateral paralysis of the sixth nerve and peripheral neuropathy. He was given a regular ward diet, but on the next day complete ophthalmoplegia had developed. At this point autoclaved vegex was given, supplemented on the following day by a high vitamin B diet plus thiamine hydrochloride administered parenterally. Under this regimen, the ophthalmoplegia improved in one day and was entirely cleared in three days. The delirium likewise subsided and was replaced by a residual Korsakoff syndrome.

This case illustrates the following points:

1. Inadequacy of a regular ward diet when a patient is in delirium.

2. Prompt response of ophthalmoplegia to thiamine hydrochloride.

3. Presence of a Korsakoff syndrome when the delirium has cleared completely and its lack of response to thiamine hydrochloride.

CASE 24.—A man aged 33, alcoholic, entered the hospital in delirium, with complete ophthalmoplegia, peripheral neuropathy and nicotinic acid deficiency stomatitis. Marked diarrhea was apparent, but how long this had been present prior to admission could not be determined. On the basal diet, the patient grew worse, and nicotinic acid deficiency encephalopathy developed. The picture otherwise remained unchanged. Three days later he was given a high vitamin B diet, vegex and thiamine hydrochloride. The nicotinic acid deficiency encephalopathy and the ophthalmoplegia improved immediately and had entirely disappeared three days later.

This case illustrates the following points:

1. Greater need for vitamins in the course of a delirium and development of a deficiency syndrome (nicotinic acid deficiency encephalopathy) in a delirious person who was fed a basal diet.

2. Prompt response of nicotinic acid deficiency encephalopathy to nicotinic acid (contained in the high vitamin B diet and vegex).

3. Prompt response of the ophthalmoplegia to thiamine hydrochloride. It has previously been noted that the ophthalmoplegia does not respond to nicotinic acid. It seems fair, therefore, to relate the disappearance of the ophthalmoplegia in this case to the added thiamine hydrochloride in the diet, and not to the nicotinic acid.

CASE 25.—A man aged 49, alcoholic, was admitted in coma. He was given the usual fluids, 5 per cent dextrose in physiologic solution of sodium chloride, and recovered from coma in twelve hours. At this point vegex and fluids high in vitamins were added to the diet, with immediate improvement in lateral motions of the eyes. Sodium nicotinate was then added, but did not further influence recovery. At this point thiamine hydrochloride was added to the diet, and the ophthalmoplegia completely disappeared in three days, as did the delirium.

This case illustrates the following points:

1. Development of ophthalmoplegia in a delirious person who was receiving an apparently normal diet.

2. Prompt response of the ophthalmoplegia to thiamine hydrochloride and inability of nicotinic acid to enhance this response.

CASE 26.—A man aged 34, alcoholic, was admitted in a dull, confused state, with bilateral paralysis of the sixth nerve and peripheral neuropathy. In addition, physical and roentgen examinations showed definite evidences of massive bilateral pneumonia. On feedings of fluids high in vitamins, the patient went into active delirium the following day, at which time sodium nicotinate was given, with no change in either the delirium or the ophthalmoplegia. A day later the patient's dietary was supplemented with thiamine hydrochloride. The ophthalmoplegia improved in one day and completely disappeared in three days. Nevertheless, the delirium persisted, and the patient eventually died of overwhelming pneumonia.

This case illustrates the following points:

1. Response to thiamine hydrochloride of the ophthalmoplegia, which, despite the ultimate fatal outcome, did not return.

2. Development of delirium in the course of an acute infection. Except that delirium tremens occurs in cases of habitually severe and chronic alcoholism and

TABLE 7.—*High Vitamin Diet with Added Thiamine Hydrochloride*

Case No., Age, Sex	History of Alcoholism	Mental Status on Admission	Neurologic Status on Admission	Treatment	Results of Treatment
23 52 yr. Male	Alcoholic	Confabulatory delirium	Bilateral paralysis of 6th nerve; peripheral neuropathy	Regular ward diet	After 1 day complete ophthalmoplegia developed
				Autoclaved vegex	Ophthalmoplegia improved in 1 day and cleared entirely in 3 days
				High vitamin B diet, thiamine hydrochloride	Delirium cleared and was replaced by a Korsakoff syndrome
24 33 yr. Male	Alcoholic	Delirious	Complete ophthalmoplegia; peripheral neuropathy	Basal diet	The stomatitis and diarrhea present on admission grew worse and nicotinic acid deficiency encephalopathy developed after 3 days
				High vitamin B diet, vegex, thiamine hydrochloride	After 3 days ophthalmoplegia and encephalopathy cleared, and a chronic Korsakoff syndrome appeared
25 49 yr. Male	Alcoholic	Comatose	Comatose	Fluids, dextrose and saline solution by vein and mouth	Patient came out of coma in 12 hours
				Regular ward diet	After 2 days the patient went into active delirium, and bilateral paralysis of 6th nerve developed
				High vitamin fluids	Improvement in lateral movements of eyes
				Sodium nicotinate	No change in the mental or neurologic picture
				Thiamine hydrochloride	Ophthalmoplegia improved in 1 day and cleared in 3 days; delirium and peripheral neuropathy remained the same; patient died of overwhelming pneumonia
26 34 yr. Male	Alcoholic	Dull, confused	Bilateral paralysis of 6th nerve; peripheral neuropathy	High vitamin fluids	Patient had a massive bilateral pneumonia and became delirious in 1 day
				Sodium nicotinate and nicotinic acid	No change in mental or neurologic picture
				Thiamine hydrochloride	Ophthalmoplegia improved in 1 day and cleared in 3 days; delirium and peripheral neuropathy remained the same; patient died of overwhelming pneumonia
27 40 yr. Female	Nonalcoholic; history of refusing to eat	Confused, stuporous	Complete ophthalmoplegia; ataxia; peripheral neuropathy	Regular ward diet	Condition was unchanged
				High vitamin diet	After 2 days slight improvement in the ophthalmoplegia, and the patient grew somewhat clearer mentally
				Thiamine hydrochloride, nicotinic acid	Marked improvement in ophthalmoplegia in 2 days, with complete clearing in 3 days; sustained for 6 more days, when patient had sudden temperature rise and died on 9th day

that it frequently follows injuries, operations and acute infections, little is known of the actual etiologic factors. This lack of consideration of precipitating and complicating factors in alcoholic delirium is one of the major reasons for discrepancies in reported mortality rates.

CASE 27.—A woman aged 40, who was not alcoholic, was admitted to the hospital in a confused, stuporous state. A history obtained from neighbors indicated that the patient had been depressed for a long period and often refused to eat for days at a time. On admission, she showed complete ophthalmoplegia, ataxia and peripheral neuropathy. Fundoscopic examination revealed numerous retinal hemorrhages (there was no evidence of hypertension, arteriosclerosis or nephritis). With a regular ward diet the condition was unchanged. On a high vitamin diet (two days) the patient grew somewhat clearer mentally and there was minimal improvement in the ophthalmoplegia. At this point thiamine hydrochloride and nicotinic acid were added. There were marked improvement in the ophthalmoplegia in two days and complete disappearance in three days. In addition, the patient became much more alert. This improvement was sustained for six more days, when she suddenly had a high temperature (109 F.) and died. Unfortunately, permission for autopsy was not obtained, so that a true final diagnosis could not be made.

This case illustrates the following points:

1. Marked improvement of the stuporous state with thiamine hydrochloride and nicotinic acid.

2. Disappearance of the ophthalmoplegia when the dietary was supplemented with thiamine hydrochloride.

STATISTICAL DATA AND COMMENT

1. Of the 27 reported cases, 3 were those of nonalcoholic patients (2 depressed persons who refused to eat and 1 with pulmonary tuberculosis and associated vomiting). The other 24 cases were of persons with chronic alcoholism. The modern trend with regard to the cause of the "alcoholic" psychoses is away from the older assumption of a direct toxic action of alcohol on the nervous system, and more in favor of a generalized metabolic defect, or more specifically an avitaminosis, caused by the chronic ingestion of alcohol. This belief is contributed to in large part by the following factors: (*a*) The dietary of alcoholic persons is deficient in vitamins. (*b*) The increase in total metabolism which occurs in alcoholic states (more particularly after delirious episodes, which frequently precede the development of the Wernicke syndrome) requires a larger supply of vitamins. At such a time relative or absolute deficiencies may appear which might not otherwise be present. (*c*) Alcoholic persons have impaired gastrointestinal absorption, usually because of associated gastritis and hepatitis. As a result, they do not completely absorb even the small amounts of food which they do eat. In addition, it is likely that the liver plays a major role in vitamin metabolism and utilization, and if this organ is in any way injured the normal utilization of the vitamins is impaired.

Our 3 reported cases of the syndrome in abstainers and those reported by others indicate clearly that chronic alcoholism is not necessary to the development of this syndrome. Its frequent association with chronic alcoholism and the fact that in all the reported cases the disease has occurred in malnourished persons suggest that the Wernicke syndrome is of nutritional rather than of toxic or alcoholic origin. This concept receives additional support from the experimental work of Alexander,[41] Zimmerman [20] and Prickett,[9] who were able to reproduce the lesion experimentally in thiamine-deficient pigeons, dogs and rats.

2. In 25 of 26 cases (the chart in 1 case was incomplete) peripheral neuropathy was present, and in every instance this syndrome preceded or accompanied the ophthalmoplegia. In no instance did the ophthalmoplegia precede the development of peripheral neuropathy. The latter syndrome in the alcohol addict and in cachectic persons is now generally accepted as clinical evidence of thiamine deficiency. The fact that this syndrome antedated or accompanied the ophthalmoplegia in every instance tends to confirm Alexander's contention that smaller amounts of thiamine hydrochloride are required to protect against angiodegeneration than are necessary to preserve the functional integrity of the peripheral nerves.

3. In addition to peripheral neuropathy, the following deficiency states were observed:

(*a*) Nicotinic acid deficiency encephalopathy, 9 cases (1, 2, 3, 6, 7, 10, 11, 12 and 24).

(*b*) Nicotinic acid deficiency, stomatitis, 9 cases (9, 11, 12, 13, 14, 18, 20, 22 and 24).

(*c*) Nicotinic acid deficiency dermatitis, 3 cases (11, 13 and 22).

(*d*) Riboflavin deficiency,[42] 1 case (22).

Whenever appropriate specific therapy was given early enough, improvement or cure resulted. We doubt whether this represents a complete list of the various deficiency syndromes which complicate the Wernicke picture. Our clinical awareness of these deficiency states has, of course, increased greatly in the past few years, and many of our early charts are obviously deficient in this respect. The development of specific laboratory technics is helping in further clarifying this problem.

With regard to the ophthalmoplegia, 8 patients were unimproved or grew worse during their stay in the hospital. Of this number, only 2 (cases 13 and 14) received supplements of thiamine. In case 13

41. Alexander.[2d] Alexander, Pijoan and Myerson.[19]

42. Jolliffe, N.; Fein, H. D., and Rosenblum, L. A.: Riboflavin Deficiency in Man, New England J. Med. **221**:921, 1939.

the thiamine was given by mouth and may not have been properly absorbed or utilized, and in case 14 the thiamine was given with the patient moribund. Of the 19 cases in which the ophthalmoplegia improved or, more usually, cleared entirely, thiamine was given in adequate amounts in each instance. As a matter of fact, the ophthalmoplegia usually cleared much more rapidly in those cases in which thiamine hydrochloride was given parenterally. Nicotinic acid was tried in 9 cases (2, 9, 13, 14, 18, 20, 22, 25 and 26), apparently without any appreciable effect on the ophthalmoplegia. In 1 case (14) pyridoxine hydrochloride was given parenterally, again without effect.

5. Nineteen patients (cases 3, 4, 7, 8, 9, 11, 13, 14, 16, 17, 18, 19, 20, 21, 22 [at home], 23, 25, 25 [after admission] and 26) entered the hospital in delirium or were delirious at some time during their stay in the hospital. We believe that delirium is a factor of considerable importance in the production of nutritional deficiencies, so far as the accompanying increase in psychomotor activity markedly raises the metabolic requirements. Up to the present, we have been unable to relate the delirium to any specific vitamin deficiency and feel that our results show clearly that delirium is not related to a deficiency in thiamine or nicotinic acid. Nonetheless, we wish to emphasize the fact that these substances should be given patients in delirium in order to prevent the development of such complications as peripheral neuropathy, ophthalmoplegia and nicotinic acid deficiency encephalopathy. The claims of more authors that the mortality rate is diminished when these substances are used are more than likely based on the fact that they present development of such complicating syndromes.

6. Fourteen patients (cases 1, 2, 5, 9, 10, 12, 13, 14, 15, 17, 18, 22, 25 and 27) entered the hospital in a stuporous condition or showed such a condition while under observation. This stuporous state in patients with the Wernicke syndrome has usually been attributed to the changes in the periventricular gray matter surrounding the third ventricle and the hypothalamic region. Such a thesis, however, takes no account of the cortex in the genesis of consciousness and bridges too many gaps in actual knowledge to become acceptable in evidence. Furthermore, cortical changes have been described in cases of the Wernicke syndrome, and it is well known that a deficiency in thiamine will interfere with cortical metabolism (and therefore function) even though no histopathologic changes are demonstrable. It has now been generally accepted that functioning of the brain is dependent on a carbohydrate substrate, an adequate supply of oxygen and various enzyme and coenzyme systems. Among the more important of these systems are cocarboxylase (the diphosphoric ester of thiamine), nicotinic acid and riboflavin. In addition, there are numerous other enzymes and vitamins

the exact identity and function of which are still under observation. A disturbance in any of these might conceivably be concerned with a disturbance in cerebral function and consciousness.

Regarding the results of therapy on this stuporous condition no definite conclusions can be drawn. In some cases thiamine seemed to help, in others nicotinic acid and in others neither. These data emphasize the importance of controlled observations in this field.

7. Ataxia of movement or speech (dysarthria) was present in 10 cases (8, 10, 12, 13, 15, 16, 18, 20, 21 and 27) and, except in case 15, showed little or no response to the various forms of therapy employed. We should hesitate, however, to draw any conclusions regarding this particular sign. In the first place, it is frequently difficult to obtain the cooperation of these mentally ill patients in the various necessary tests, and they are almost invariably too sick for testing of their gait. Furthermore, ataxia as a sign has no localizing value and may be the result of involvement of the peripheral nerves, the spinal cord, the cerebellum, the extracerebellar nuclei or even the frontal lobe. We can definitely state, however, that ataxia and ophthalmoplegia do not necessarily always coexist in the same patient and that the ataxia certainly does not show the same dramatic response to thiamine as does the ophthalmoplegia. The production of a cerebellar syndrome by Pappenheimer and Goettsch [10] in chicks fed a vitamin E–deficient diet is a lead well worth following. Unfortunately, none of our patients received vitamin E, and we can therefore add nothing by way of confirmation or denial. However, 1 patient under our observation, with a so-called alcoholic cerebellar syndrome and marked ataxia of four years' duration, has shown marked improvement on a high vitamin, high calory diet supplemented by large amounts of thiamine hydrochloride, nicotinic acid and vitamin E. While this offers no specific leads, it does not indicate that the condition is not necessarily irreversible.

Our patients invariably had nystagmus, usually most marked after the ophthalmoplegia had cleared. This sign was not appreciably affected by any specific therapy, but usually gradually disappeared.

8. Fourteen of the patients eventually died, 7 of associated infections which in themselves were sufficient cause for death: patient 3 of pneumococcic pneumonia; patient 6, of pulmonary tuberculosis; patient 11, of erysipelas; patient 12, of bronchopneumonia; patient 17, of toxic hepatitis; patient 18, of bronchopneumonia, and patient 26, of pneumococcic pneumonia. The difficulties in preventing and combating infection in undernourished persons are well known. Furthermore, infection, with its resultant elevation of temperature, increases the metabolic (vitamin) needs of the patient and aggravates latent deficiency states. As a result, the prognosis in such cases is markedly altered for the

worse. Of the others, most of the deaths occurred among persons who were inadequately treated from a nutritional standpoint.

9. Of the 13 patients who did not die, 12 were left with a residual Korsakoff syndrome (cases 4, 5, 8 and 10, in which it eventually cleared, and 15, 16, 19, 20, 21, 22, 23 and 24). Of the 12 patients, 9 were admitted to the hospital in delirium and 3 (cases 5, 10 and 15) in stupor. Three received a regular ward diet (ample in all vitamins), 1 received a high vitamin, high calory diet and parenteral injections of liver extract (case 10, in which the syndrome eventually cleared), 3 received a basal diet and thiamine hydrochloride, 2 received a regular diet and thiamine hydrochloride, 1 received a regular diet, nicotinic acid and thiamine hydrochloride and 1 received a high vitamin B diet plus vegex and thiamine hydrochloride. Patient 25, who received vegex, fluids high in vitamins, sodium nicotinate and thiamine hydrochloride, was the only one to recover in whom a Korsakoff syndrome did not develop. The problem of the cause of the Korsakoff syndrome and its response to therapy is too complicated for consideration here, but these data indicate clearly (1) that most of the recovered patients are left with a residual Korsakoff syndrome and (2) that thiamine hydrochloride is not specific in the treatment of this syndrome, although it may help in effecting eventual recovery.

CONCLUSIONS

Twenty-seven cases of Wernicke's syndrome (3 of which occurred in nonalcoholic patients) are analyzed and the following conclusions reached:

1. The syndrome as originally described by Wernicke is probably a combination of several nutritional deficiencies affecting the nervous system and need not necessarily be complete in any case. It is of course possible that the exact syndrome which Alexander has reproduced experimentally in pigeons may on occasion occur in uncomplicated fashion in man, but except for ophthalmoplegia, the other symptoms would be difficult to evaluate from a purely clinicopathologic point of view.

2. Our results indicate that (*a*) the ophthalmoplegia is a thiamine deficiency, (*b*) the clouding of consciousness may be related to anything which interferes with proper cerebral metabolism, some of the known offenders being lack of carbohydrate, lack of oxygen, lack of thiamine or nicotinic acid or riboflavin or of all three and probably a lack of many other substances now under investigation, and (*c*) the ataxia is difficult to evaluate and its response to therapy has not as yet been worked out.

3. Other deficiency syndromes may and do superimpose themselves on the more usual Wernicke picture, and these require specific treatment.

4. The ophthalmoplegia is invariably preceded or accompanied by peripheral neuropathy. This tends to confirm Alexander's thesis that smaller amounts of thiamine are necessary to prevent the polioencephalopathic changes than are necessary for antineuritic action.

5. Delirium, with its marked increase in psychomotor activity, and hence in total metabolism, frequently precedes the development of this syndrome.

6. In the recovered patients, the development of a Korsakoff syndrome is the rule. This does not show a consistent response to thiamine hydrochloride, as has frequently been claimed.

7. The use of such terms as the Wernicke syndrome and encephalopathia alcoholica for the encephalopathic states which complicate alcoholism and other conditions leading to disturbed nutrition, while justified, has certain limitations. We believe that in each case of such disorder the clinical signs or syndromes presented, the response of these phenomena to specific therapeutic agents recorded and finally, the metabolic and pathologic changes correlated with the clinical picture found during life should be indicated. Bender and Schilder [2c] were able to correlate the clinical picture seen in the Wernicke syndrome with the postmortem observations. Alexander,[41] utilizing the experimental approach has focused attention on the essential nutritional disturbance. We have presented certain nutritional and metabolic aspects of the problem. Similar correlated studies will undoubtedly lead to a much better understanding of the nutritional and metabolic disorders which interfere with the functional economy of the nervous system.

The thiamine hydrochloride, nicotinic acid, nicotinic acid amide and pyridoxine hydrochloride used in this study were supplied by Merck & Co., Inc.; the vegex was furnished by Vegex, Incorporated, and the liver residue and liver fractions were supplied by the Lederle Laboratories, Inc.

THE ELECTROENCEPHALOGRAPH AS AN AID IN THE STUDY OF NARCOLEPSY

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A heterogenous group of disorders characterized by unusual drowsiness or attacks of irresistible sleep, occurring during the day, are frequently classified under the narcolepsies. A certain number of such narcoleptic patients have, in addition, attacks of muscular weakness and loss of muscle tone, a condition referred to as cataplexy [1]; these attacks usually follow emotional experiences, such as hearty laughter, anger or surprise. That there is a relation between narcolepsy and cataplexy is generally conceded, although the mechanism is not understood. There are various theoretic explanations for the phenomena of sleep, but none is completely satisfactory.

Both narcolepsy and cataplexy appear to be symptoms rather than disease entities. Most clinicians are familiar with episodes of somnolence occurring in association with encephalitis, tumor of the brain, syphilis, endocrinology, blood dyscrasias, epilepsy, chronic systemic disease and the psychoneuroses. It is not the purpose of this paper to discuss in detail the symptomatology and pathology of the narcoleptic and the cataplectic disorders. We would refer the reader to outstanding articles by Wilson,[2] Adie,[3] Redlich,[4] Levin [5] and Daniels.[6]

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1. Webster defines cataplexy as "increased muscular rigidity." However, Adie and Wilson (Neurology, edited by A. N. Bruce, Baltimore, William Wood & Company, 1940) have used the term cataplexy to describe those states of muscular powerlessness following emotional experiences, in contradistinction to the more common term catalepsy, which is employed to designate the state of muscular rigidity seen predominantly in catatonic schizophrenia, hysteria and the hypnotic trance.

2. Wilson, S. A. K.: (*a*) The Narcolepsies, Brain **51**:63-109 (March) 1928; (*b*) Neurology, edited by A. N. Bruce, Baltimore, William Wood & Company, 1940.

3. Adie, W. J.: Idiopathic Narcolepsy: A Disease Sui Generis, with Remarks on the Mechanism of Sleep, Brain **49**:257-306 (Sept.) 1926.

(Footnotes continued on next page)

The clinical histories of the cases forming the basis of this paper are summarized in the table.

We are particularly interested in the study of the narcolepsies by means of the electroencephalograph. There are many who tend to see a relation between epilepsy and narcolepsy. Wilson [2b] stated that the resemblances are often greater than the differences and stressed "periodicity, recurrence, abrupt onset, interference with the stream of consciousness, brevity, often quick return to normal" as points of similarity. Adie expressed the belief that no patient with attacks of sleep and cataplexy "has ever become epileptic in the ordinary sense, although some of them have been narcoleptic for twenty, thirty, and in some cases forty years." The failure of narcoleptic persons to respond to treatment with bromides, phenobarbital and other sedatives indicates a difference rather than a similarity between the two disorders. It is noteworthy that narcolepsy is partially or completely controlled by such stimulating drugs as ephedrine and amphetamine, whereas epilepsy is best treated by sedatives.

Since the electroencephalograph has been of considerable aid in the investigation of the epileptic disorders,[8] we have studied a series of 22 narcoleptic patients with this instrument during the past year. The electroencephalographic technic is of definite help in the study of narcolepsy and also yields evidence of dissimilarity between narcolepsy and epilepsy. There is nothing in the character of the electrical discharges from the brain of the narcoleptic patient which would link them with the abnormal electrical discharges from the brain of the epileptic patient. Clinically there is little difference between the sleep of a narcoleptic patient during an attack and the ordinary nocturnal sleep of a normal person, except for its sudden, irresistible, and at times inappropriate occurrence. The electroencephalogram confirms this clinical observation, in that, as previously observed by Gibbs and Gibbs,[8] Gibbs, Davis and Lennox [9] and Jansen,[10] it showed no apparent difference between the electrical discharges from the brains of certain patients with narcolepsy

4. Redlich, E.: Epilegomena zur Narkolepsiefrage, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:128-173, 1931.

5. Levin, M.: Narcolepsy (Gelineau's Syndrome) and Other Varieties of Morbid Somnolence, Arch. Neurol. & Psychiat. **22**:1172-1200 (Dec.) 1929.

6. Daniels, L. E.: Narcolepsy, Medicine **13**:1-122 (Feb.) 1934.

7. Adie, W. J.: The Clinical Features of Idiopathic Narcolepsy, Practitioner **125**:288-295 (Aug.) 1930.

8. Gibbs, E. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Company, 1941.

9. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electroencephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133-1148 (Dec.) 1935.

10. Jansen, R.: Hirnbioelektrische Untersuchungen über den physiologischen Schlaf und den Schlafanfall bei Kranken mit genuiner Narkoplesie, Deutsche Ztschr. f. Nervenh. **149**:93-106, 1931.

Clinical Data on Twenty-Two Patients with Narcolepsy

Case No.	Sex	Age at Onset, Yr.	Type of Narcolepsy *	Duration of Narcolepsy	Handicap (Sleep)†	Cataplexy †	Head Injury	History of Influenza or Encephalitis	Body Build	Neurologic Symptoms and Signs	Therapy	Benefit from Therapy †
1	F	13	I	17	++	+++	0	0	Normal	0	Ephedrine..... Amphetamine sulfate, 10-15 mg.	+ +++
2	M	13	I	5	+++	++	0	0	Normal	0	Amphetamine.....	?
3	M	14	I	13	+++	++	0	0	Slender	0	Thyroid..... Amphetamine, 20-30 mg.	0 +++
4	M	18	I	14	++	++	2 yr. before	0	Obese	0	Amphetamine, 30-40 mg.	++
5	M	15	I	20	++	+	0	0	Normal	Unequal pupils	Amphetamine, 20 mg....	+++
6	M	9	I	10	++	++	0	0	Mildly obese	0	Amphetamine, 10/20 mg.	+++
7	F	9	I	19	+	++	0	0	Obese	0	Amphetamine, 7.5 mg...	++++
8	F	17	I	6	+++	+++	0	0	Slender	0	Amphetamine, 5 mg.....	+++
9	M	17	I	12	+++	++	2 yr. before	Influenza 1918	Obese	0	Amphetamine.....	?
10	M	11	I	11	+++	+++	1 yr. before	0	Obese	..	Amphetamine.....	++
11	M	18	I	35	++	0	0	Typhoid at 18	Slender	0	Amphetamine, 10-20 mg.	++
12	M	10	I	15	+++	+++	0	0	Slender	..	Amphetamine, 20-30 mg.	+++
13	M	10	I	12	+++	++	2 yr. before	0	Obese	..	Amphetamine, 50-60 mg.	++
14	F	33	I	3	+++	++++	0	0	Normal	..	Ephedrine..... Amphetamine, 20-30 mg.	0 ++
15	F	14	I	18	++	.....	.....					
16	M	11	I	7	+++	++	0	Postvaccination headache and confusion at 6 yr. of age	Obese	0	Amphetamine, 2-4 mg...	++
17	M	16	..	15	++	0	0	0	Slender	0	Amphetamine, 2-3 mg...	+
18	M	42	S	6	+	0	0	Encephalitis	Slender	Parkinsonian	Stramonium..... Amphetamine, 50-60 mg.	++ +
19	M	18	S	21	++	0	0	Lead encephalitis (?)	Slender	Facial Weakness of lead colic ?	Calcium..... Amphetamine, 10/20 mg.	0 ++
20	M	30	S	3	++	0	Basal fracture	0	Obese	Migraine and epilepsy	Phenobarbital, 2 grains (0.124 Gm.) Amphetamine, 10-20 mg.	++ 0
21	M	42	S	2	++++	0	0	Influenza 1918	Normal	Depressed; parkinsonian signs	Stramonium..... Amphetamine.....	0 0
22	F	26	S	5	++	0	0	0	Normal	..	Amphetamine, 1 mg.....	0

* I indicates the idiopathic type; S, the symptomatic.
† Graded from 1 to 4; + means minimum; ++++, maximum.

during an attack and the electrical discharges from the brain of a sleeping person. This points to a sleep mechanism in the case of the narcoleptic patient which is abnormal only in its facilitation.

Four clearly defined stages in the electroencephalographic tracings of physiologic sleep have been described by Loomis, Harvey and Hobart.[11] In a later investigation in which these authors collaborated with Davis and Davis,[12] they subdivided the second stage into two substages. The stages are as follows:

A: alpha rhythm—the waking record (eyes closed).

B_1: low voltage; normal (alpha) rhythm lost—intermediate stage.

B_2: low voltage; slow (delta) waves appearing—intermediate stage, merging into sleep.

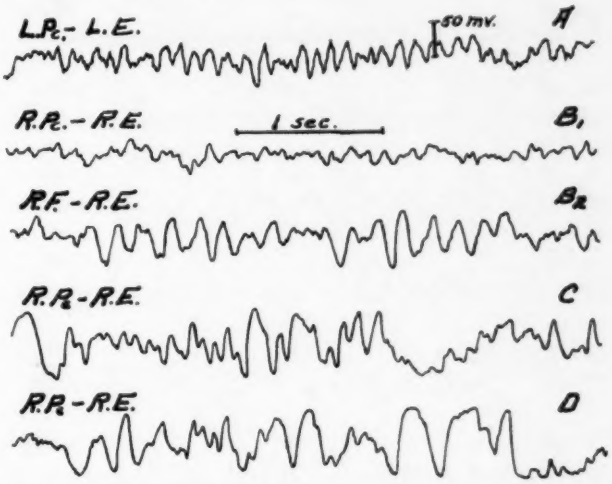

Fig. 1.—The waking stage, sample *A*, and the first three sleeping stages, samples B_1 and B_2, *C* and *D*, of normal physiologic sleep. In the B_1 stage the amplitude of the 9 per second cycles present in the A stage has diminished. In the B_2 stage there have developed slowing of the frequency pattern to 5.5 cycles per second and an increase in their amplitude. An entirely different pattern has developed in the C stage. Random slower cycles with still greater amplitude appear, in addition to the characteristic 14 to 15 per second cycles, called "spindles." In the D stage the slow cycles have increased in number; their wavelength has increased, and the "spindles" are less prominent.

C: 14 to 15 per second spindles and moderately slow waves—real sleep.

11. Loomis, A. L.; Harvey, E. N., and Hobart, G.: Cerebral States During Sleep, as Studied by Human Brain Potentials, J. Exper. Psychol. **21**:127-144 (Aug.) 1937.

12. Davis, H.; Davis, P. A.; Loomis, A. L.; Harvey, E. N., and Hobart, B.: Changes in Human Brain Potentials During the Onset of Sleep, Science **86**:448-450 (Nov. 12) 1937.

D: spindles plus random waves; both types of waves increase and the slow waves become slower.

E: random waves; the spindles become inconspicuous, but slow waves continue to increase in voltage and in wavelength.

The first four stages are illustrated in figure 1. As the same stages are found in the electroencephalographic records of narcoleptic persons,

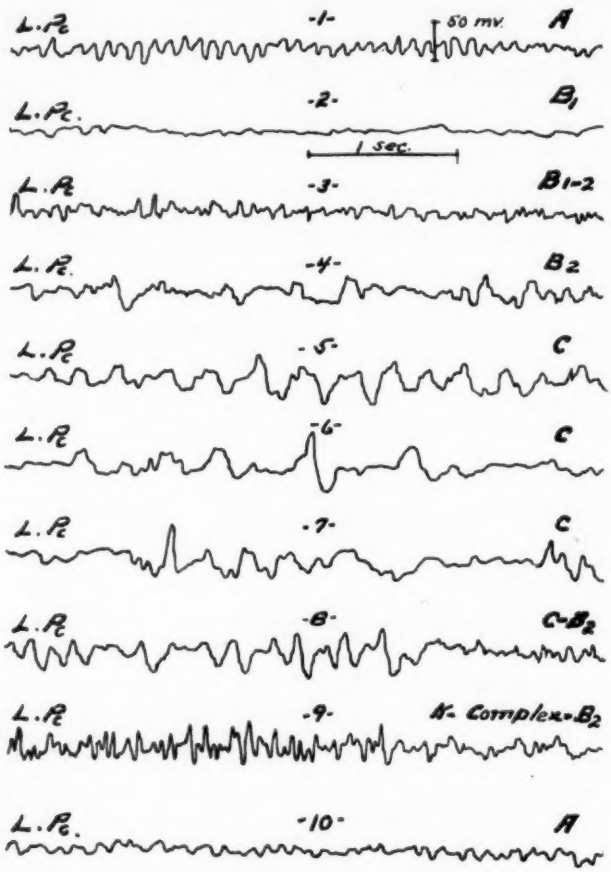

Fig. 2.—This figure illustrates how the record oscillates from one stage to another during a single narcoleptic attack of ten minutes: (*1*) a normal waking record; (*2*) flattening out of the pattern in a typical early B stage, i. e., the B_1 stage; (*3*) appearance of low voltage, 5 to 6 per second slow cycles and some ripples of 20 to 22 per second cycles, sometimes but not always seen in the B_2 stage of physiologic sleep; (*4*) deeper B_2 stage, approaching the C stage in its qualities; (*5, 6* and *7*) three types of early C stages, in which the "spindles" have not reached full maturity; (*8*) stage of waking, showing slow cycles, the frequencies of which correspond to the C (3 per second) and B (4 to 7 per second) stages; (*9*) B stage, similar to that in *3*, with the additional presence of a rapid, high amplitude frequency pattern, a response to some sound stimulus and frequently observed in normal sleep; (*10*) period following the narcoleptic attack.

it will be convenient to use these stages in describing the electroencephalograms of the narcoleptic patients in this study. It should be pointed out, however, that this grouping of electroencephalographic patterns has its limitations in that patterns are frequently encountered which do not fit easily into any one of the five stages. This is true not only of the sleep of narcoleptic persons, but, from our experience, of physiologic sleep as well. The number of stages appearing in the different narcoleptic attacks of the same patient varied with the depth of sleep in each attack. Figure 2 (electroencephalographic record in case 1) illustrates how the record oscillates from one stage to another in a single narcoleptic attack. As in physiologic sleep, the potentials from homologous areas of the two hemispheres tend to be symmetric, except for

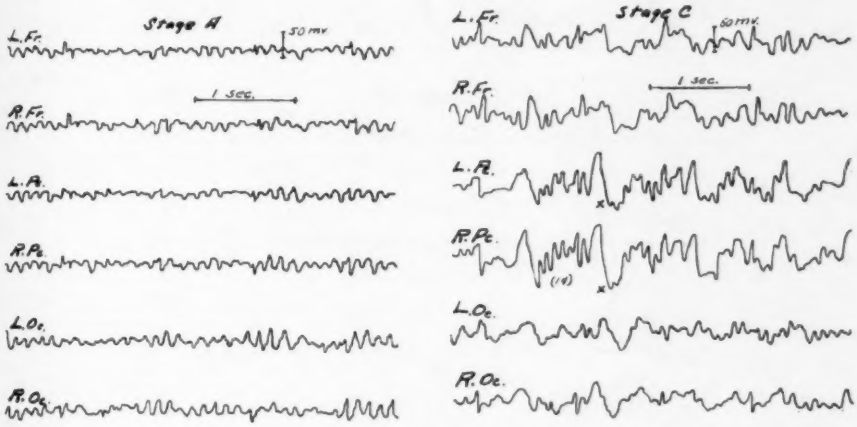

Fig. 3 (case 2).—Simultaneous recordings from the frontal, precentral and occipital regions of the two sides during the waking state, stage A, and during a narcoleptic attack, stage C. In stage C, (*14*) indicates characteristic 14 per second spindles; *x*, the K complex.

the occipital lobes, where asymmetry is the rule in the normal waking and sleeping states and in the narcoleptic state. The brain potentials in case 2 taken from homologous areas before and during deep narcoleptic sleep by the use of six simultaneously recording pens are illustrated in figure 3.

In a group of 22 patients with symptoms of narcolepsy, 17 had normal waking records (table, cases 1 to 17). Sixteen of these patients had narcoleptic attacks during the electroencephalographic recording, and the patterns which developed during these attacks were in all instances similar to those observed during physiologic sleep. For the remaining

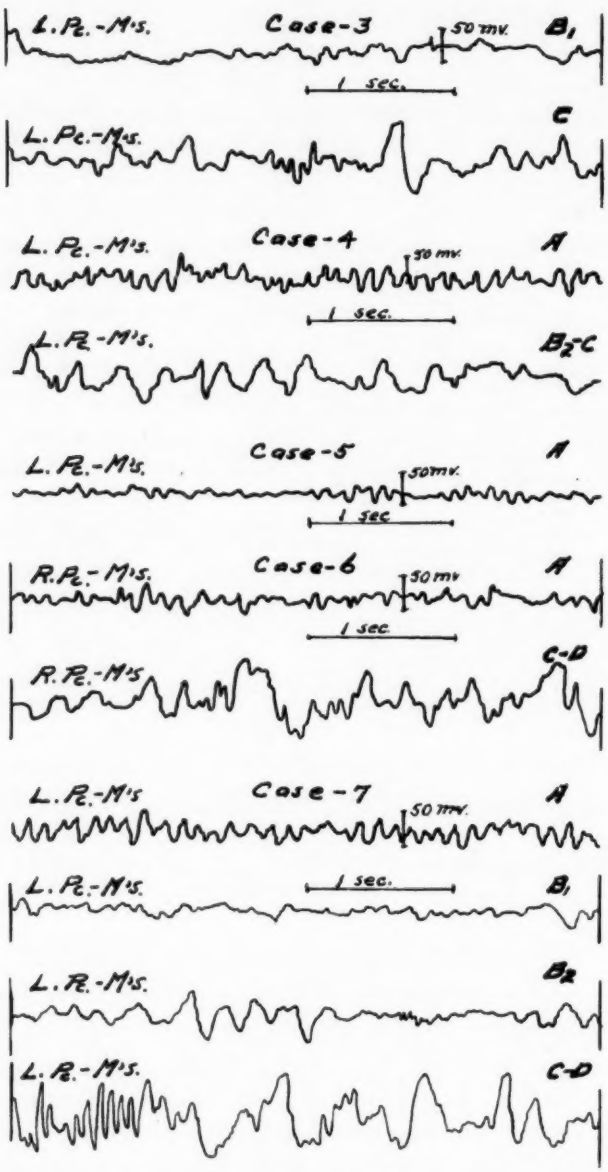

Fig. 4.—Samples of electroencephalographic tracings of narcoleptic patients (see text for description).

5 patients (table, cases 18 to 22) the electroencephalographic tracings were atypical or abnormal. In none of these did narcoleptic attacks develop during the electroencephalographic recording, and none of them showed changes in the quality of the record resembling the electroencephalographic patterns of physiologic sleep. Brief descriptions of the

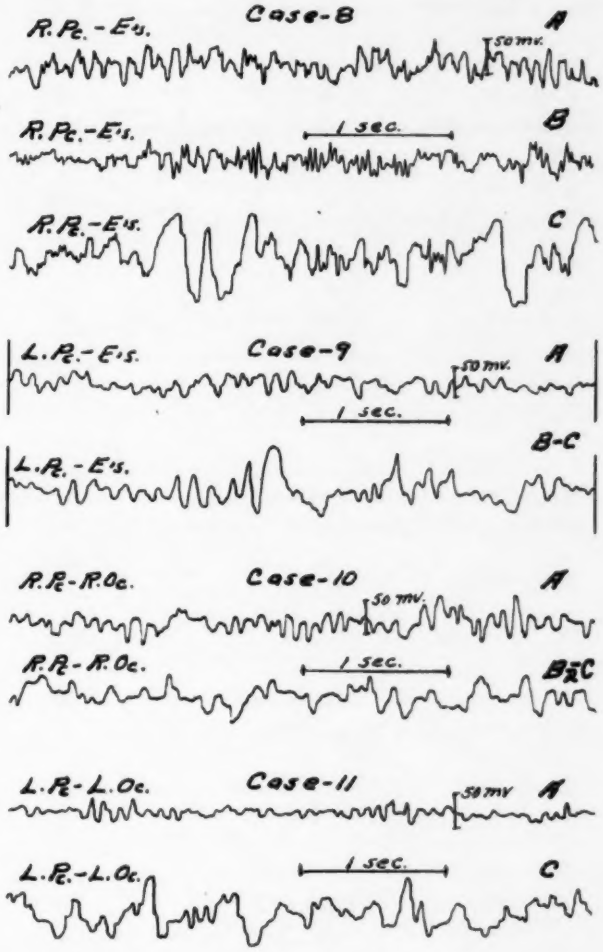

Fig. 5.—Samples of electroencephalographic tracings of narcoleptic patients (see text for description).

electroencephalographic tracings (figs. 4, 5 and 6) from the first 17 narcoleptic patients (table) follow. The tracings from cases 1 and 2 are illustrated and described in figures 2 and 3, respectively.

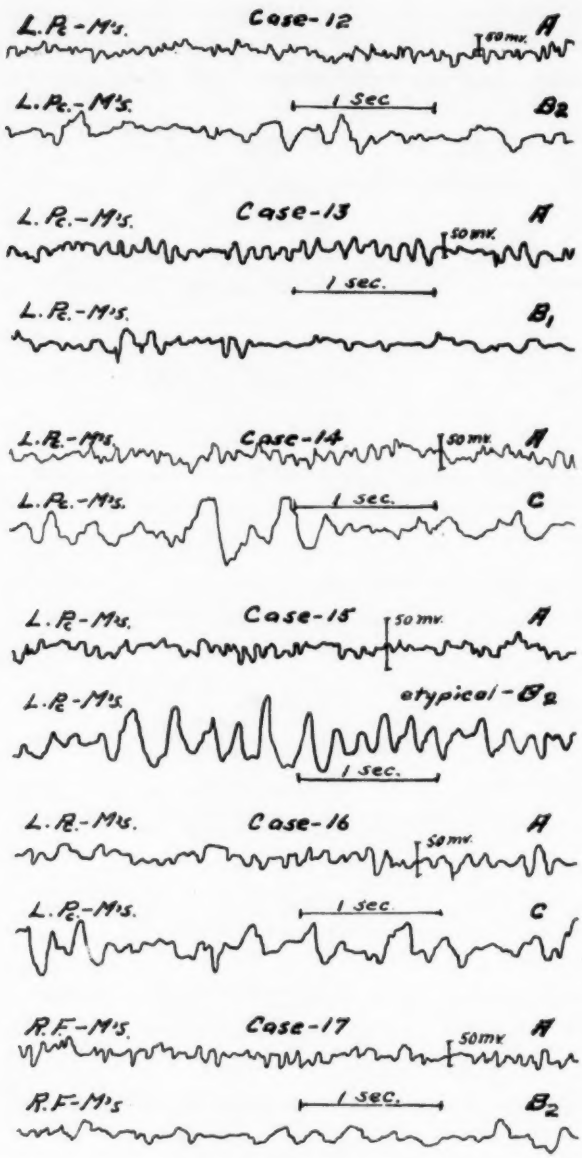

Fig. 6.—Samples of electroencephalographic tracings of narcoleptic patients (see text for description).

SUMMARY OF CASES

CASE 3.—The patient's narcoleptic attack lasted the entire twenty-five minute recording period. We probably did not obtain a sample of the waking record. Stages B_1 and B_2, C and D occurred. Two stages, B_1 and C, are illustrated (fig. 4, *case 3*). In the C stage are random slow cycles and the 14 per second spindles, the latter being typical of physiologic sleep (fig. 1). In parts of the record there were momentary bursts of rapid activity, with a frequency of about 20 cycles per second. These were seen when the pattern changed from the C to the B stage. They also occurred in the record of case 1 (fig. 2, sections *3* and *9*). Rapid potentials of this nature are sometimes seen in physiologic sleep in the drowsy or "floating" period.

CASE 4.—The patient had three short narcoleptic attacks during a fifteen minute recording period. The depth of sleep varied in the different attacks, as indicated by the electroencephalographic pattern. In the illustration (fig. 4, *case 4*) the waking pattern is shown with stages B_2 and C, during which time the patient was sleeping lightly. In the other two attacks the patient passed only into the B stage.

CASE 5.—The patient had mild narcoleptic attacks and obtained considerable benefit from amphetamine. He had taken this drug just before coming for the test. He remarked that he did not feel sleepy, and he is the only patient with a normal waking record who failed to drop off to sleep while the electroencephalographic record was being taken. His waking record is illustrated in figure 4, *case 5*.

CASE 6.—The patient's record showed frequent alteration of the stages during the thirty-five minute period of recording. Only occasionally did the waking, or A, stage appear, most of the record consisting of stages C and D. Two stages are illustrated in figure 4, *case 6*.

CASE 7.—This patient's record also showed a variety of stages over a period of forty-five minutes. During the first half of the record, the waking state, stage A, predominated (fig. 4, *case 7*), with the occasional appearance of stage B_1. The latter half of the record was about equally divided between the first four stages, the patient occasionally waking and then passing off into a deep sleep. Three stages are illustrated in the tracing. In the B_2 sample are the characteristic flat record and the 5 per second cycles. In the C and D stages are the typical 14 per second spindles and slow, high voltage cycles. The patient was sound asleep while this portion of the record was taken.

CASE 8.—The brain potentials were recorded for a period of thirty minutes. The electroencephalographic tracings indicated that the patient's narcopletic attack was of a mild nature, as most of the record showed only the stage B changes. The waking record, stage A, shows, in addition to the 10 per second frequency pattern, some traces of superimposed rapid, 25 per second, cycles (fig. 5, *case 8*). These rapid cycles replace most of the 10 per second pattern in stage B, with accentuation of their amplitude. These rapid cycles are present in a small percentage of sleep records from normal persons and are probably characteristic of this type of waking record. On only two occasions did the patient pass into stages C and D, and then only for a few seconds. Stage C is illustrated. Notice that the 25 per second cycles are greatly diminished in this stage.

CASE 9.—The patient readily dropped off to sleep and remained in this state for the greater part of seventeen minutes' recording. There was frequent oscilla-

tion of the pattern between stages B and C (fig. 5, *case 9*). At no time did the patient appear to be sound asleep.

CASE 10.—At no time over a period of fifteen minutes' recording did the patient pass into a deep sleep. Stage A and a pattern which is best labeled a combination of stages B_2 and C (fig. 5, *case 10*) are illustrated. Five per second cycles, characteristic of stage B_2, and slower cycles with scattered 14 per second spindles, characteristic of stage C are present.

CASE 11.—This record was obtained over a period of seventeen minutes. The patient passed in and out of his narcoleptic spells, as is indicated by the frequent alteration of the electroencephalographic tracings from the waking stage, A, to the sleeping stages, B and C. Stages A and C are illustrated (fig. 5, *case 11*).

CASE 12.—The patient's narcoleptic spells during the electroencephalographic record were light, as indicated by the fact that changes never passed beyond the B stage. He remained in the B stage during the greater part of this period, the electroencephalographic pattern alternating from the B_1 to the B_2 type. The waking record (stage A) has a moderately disorganized appearance, but is within normal range (fig. 6, *case 12*). In the B_2 stage there are flattening out of the waking patterns and the appearance of random 4 per second cycles, characteristic of this stage.

CASE 13.—A ten minute record was obtained. During this period the patient did not pass beyond the B_1 stage (fig. 6, *case 13*).

CASE 14.—A record of one hour was obtained on this patient. During two thirds of this period she had several narcoleptic spells, when the pattern altered from stage B to stage D. The greater part of the sleeping record was of stages B and C. Twenty per second cycles appeared when the patient passed from the A to the B or from the B to the A stage. The A and C stages are illustrated in figure 6, *case 14*.

CASE 15.—The patient had three distinct narcoleptic spells during a twenty minute recording period. In the first only the B stage was present, and in the remaining two attacks the D stages appeared. An unusual pattern recurred frequently in the last two narcoleptic spells. The frequency of this pattern was 6 cycles per second, which is characteristic particularly of the B_2 stage, but the amplitude of the individual cycles was unusually high for this stage (fig. 6, *case 15*). During physiologic sleep cycles of high amplitude are seen in the C, D and E stages. This pattern, therefore, has features characteristic of both the B_2 and the deeper stages of sleep.

CASE 16.—In a twenty minute record obtained on this patient stages A, B and C occurred. After a period of three minutes stages B and C appeared, but were frequently replaced by momentary appearances of the B_1 and A stages. Stages A and C are illustrated (fig. 6, *case 16*). In stage C there is a dominance of random slow, 3 to 4 per second cycles, with some traces of low voltage, 14 per second spindles.

CASE 17.—During the fifteen minutes of recording the patient passed into a light slumber on three occasions, during which time stages B_1 and B_2 appeared, stage B_1 being the more common. The patient's attack was obviously light. Stages A and B_2 are illustrated (fig. 6, *case 17*). The flattening out of the normal pattern and the appearance of some low voltage slow, 4 to 5 per second cycles, are clearly evident in the stage B_2 illustrated.

In 16 cases of narcolepsy the brain potentials during the narcoleptic attacks were found to resemble those of physiologic sleep. In case 5 the patient had no narcoleptic attacks while the record was being taken, probably because he had just previously taken amphetamine.

The duration of the narcoleptic attacks and the depth of sleep in each varied not only in different patients but in the same patient, as shown by the different brain potential patterns, or stages, which were recorded. Most of the patterns were comparable to those observed in sleep, but occasional atypical patterns appeared, such as the 6 per second, high voltage pattern present in case 15. As these unusual patterns are also encountered occasionally in physiologic sleep, they are believed not to be of special significance. Patterns consistent with epilepsy were not observed in any of these patients, and none of the patterns observed during the narcoleptic attacks could be induced or

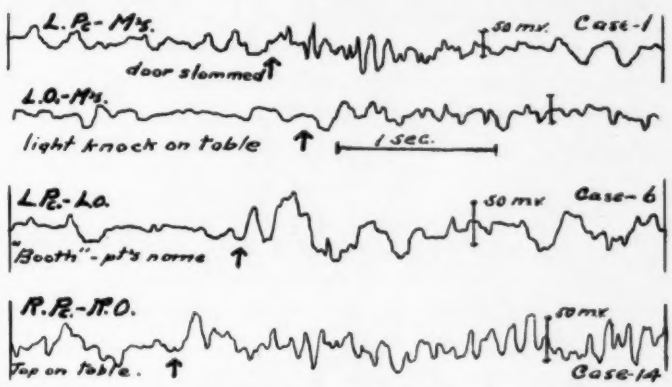

Fig. 7.—Changes in the character of the narcoleptic patterns resulting from external sound stimuli. The time and the nature of the sound stimuli are indicated on the record.

exaggerated by hyperventilation for a period of two minutes, in contradistinction to the reaction in epileptic patients.

Loomis, Harvey and Hobart [13] have demonstrated that an alteration of sleep patterns may result from a sound stimulus. They called this type of response the K complex. The K complex can occur also spontaneously (fig. 2). Alteration of the electroencephalographic pattern in response to sound is also readily demonstrated during narcoleptic sleep. Figure 7 illustrates four types of such alteration. This response of the electroencephalographic pattern is further evidence of the similarity of the brain potentials in this condition to those in physiologic sleep.

13. Loomis, A. L.; Harvey, E. N., and Hobart, G. A.: Distribution of Disturbance-Patterns in the Human Electroencephalogram, with Special Reference to Sleep, J. Neurophysiol. **1**:413-430 (Sept.) 1938.

There follows a description of the electroencephalographic tracings in the 5 cases in which alterations characteristic of physiologic sleep did not appear.

Case 18.—The brain potentials were normal except for the momentary bursts of 25 per second cycles, an atypical feature of the record.[14]

Case 19.—The record was abnormal. Random, abnormally slow cycles with plateau contour and superimposed rapid cycles were common (*x, case 19,* fig. 8).

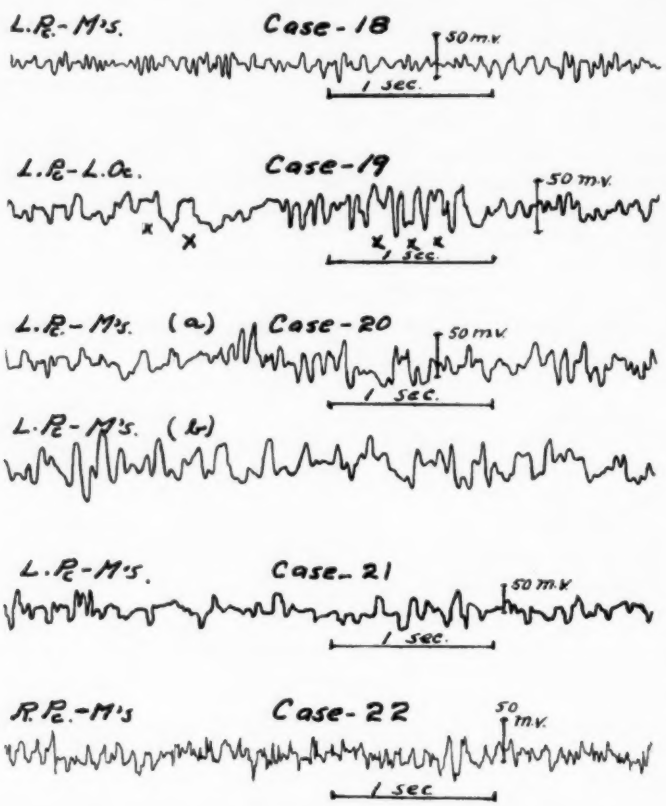

Fig. 8.—Tracings of the 5 patients whose waking records were abnormal. In none of the cases were we successful in obtaining sleep patterns, as none of the patients had a narcoleptic attack during the recording.

14. Present knowledge of the significance of the rapid frequencies (beta rhythm) from the standpoint of abnormal cerebral function is relatively limited as compared with that of the slow cycles (delta rhythm), which are associated definitely with abnormal cerebral activity. Many normal records contain rapid cycles, as do also records from brains with verified pathologic changes. One is not yet able clearly to distinguish between normal and abnormal rapid activity. There can be little doubt that such a distinction exists, and it is hoped that future investigation will clarify this.

There was a notable absence of organized normal frequency cycles (cycles within 8 to 12 per second).

CASE 20.—The electroencephalographic tracings in this case were likewise abnormal. Most of the record contained a disorganized frequency pattern with many rapid and scattered slow cycles (fig. 8, *case 20*). Occasional runs of slow cycles appeared, the frequency, contour and amplitude of which lacked consistency (fig. 8, *case 20*). This type of activity is common in many known organic disorders. It was increased by hyperventilation, a fact which excludes it from the patterns associated with physiologic sleep.

CASE 21.—The record shows a lack of well organized normal frequency cycles (fig. 8, *case 21*). There are, on the other hand, no well defined slow or rapid cycles. The record is borderline in character.

CASE 22.—Considerable rapid activity is present, often superimposed on the normal cycles. It is best described as an atypical record (fig. 8, *case 22*).

In comparing the electroencephalographic tracings of the first group of 17 cases with those of the second group of 5 cases, we wish to reemphasize two distinguishing characteristics.

1. The "waking" electroencephalographic tracings of the first 17 cases are usually normal, while those of the remaining 5 cases are likely to contain atypical or abnormal elements.
2. The tracings of the first 17 cases show alterations in the pattern characteristic of sleep. The tracings of the last 5 cases show no such alterations.

An effort was made to induce a cataplectic attack while the electroencephalogram was being taken in a number of patients who had a tendency to cataplexy. We were not able to induce an attack artificially in a single instance. Although one can only speculate, it is likely that the electroencephalogram would show no definite abnormality during a cataplectic attack, as there is no loss of consciousness and the manifestations of the attack appear to be related chiefly to the peripheral neuromuscular mechanism.

COMMENT AND SUMMARY

The electroencephalographic studies on this group of narcoleptic patients confirm certain clinical views. Sixteen of the 22 patients had narcoleptic spells during the periods of electroencephalographic recording. During these periods the brain potentials became modified to resemble those observed in physiologic sleep. This confirms the clinical observation that a narcoleptic spell is due to a physiologic disturbance resulting in the facilitation of sleep. As Wilson has stated and as is generally recognized, the narcoleptic conditions are a heterogenous group of disorders. One need not be surprised, therefore, to find that brain potentials (table) do not always show a uniformity of pattern. In

17 of the 22 cases normal waking patterns occurred. In the remaining 5 cases abnormal waking patterns were present (fig. 8). In none of these 5 cases did we obtain patterns characteristic of physiologic sleep, although the clinical history led us to believe these patients had narcolepsy. The electroencephalogram being a measure of the electrical activity of the cerebrum, it is fair to assume that the basic neurophysiologic disturbance in each of these 5 cases differed. In addition these 5 cases differed from the first 17 cases. In those cases in which there was facilitation of the sleep electrical potential activity in an otherwise normal pattern (cases 1 to 17), the cerebral disturbance would appear to be limited to the neurophysiologic sleep mechanism. In the remaining 5 cases, in which abnormal records were present, the electroencephalographic studies give evidence that the neurophysiologic disturbance was more widespread. The fact that the abnormal patterns differed in these 5 cases suggests that the location or character of the lesion also differed in each case.

While electroencephalographic studies in these 22 cases indicate that patients with abnormal records are less troubled with facilitation of sleep, we do not feel justified, from the small number of cases, in concluding that this is the rule. It is evident from the table that the first 17 patients, with 1 exception, suffered from cataplectic attacks of greater or lesser severity, while the remaining 5 patients did not suffer from this symptom. The first 17 patients, with 1 exception, did not show neurologic symptoms and signs, while the remaining 5 patients did manifest such symptoms and signs.

Some clinicians have found it convenient to divide the narcolepsies into the "symptomatic" and the "idiopathic" type, recognizing that there are objections to such a classification and realizing that in the individual case it may not be possible to make the distinction. If one cares to use this clinical distinction, one might say that those patients showing normal waking electroencephalographic records fall into the "idiopathic" group, while those showing abnormal waking records are more likely to fit into the "symptomatic" group.

THE CORTICAL FREQUENCY SPECTRUM IN EPILEPSY

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The theoretic as well as the practical advantages of considering the electrical activity of the cortex in terms of a spectrum has been emphasized in earlier papers.[1] The most important of these advantages is that a spectrum reduces to an orderly arrangement a tremendous volume of data and thereby makes it comprehensible. A continuous spectrum, however, is necessary unless one is willing to discard a large part of the data.

Even before a technic was available for making this transformation, attempts were made to represent the electroencephalogram as a distribution of energy over a range of frequencies. Travis and Knott [2] plotted the mean amplitude of waves of a given duration against the frequency. Gibbs, Gibbs and Lennox [3] expressed their results in terms of energy distribution on a scale of frequency, relying for evidence as to whether the energy distribution was predominantly fast or slow on wave counts and inspection of the record. More recently, Drohocki

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1. (*a*) Gibbs, F. A.: Interepretation of the Electroencephalogram, J. Psychol. **4**:365-382, 1937. (*b*) Grass, A. M., and Gibbs, F. A.: A Fourier Transform of the Electroencephalogram, J. Neurophysiol. **1**:521-526, 1938. Gibbs, F. A.; Williams, D., and Gibbs, E. L.: Modification of the Cortical Frequency Spectrum by Changes in CO_2, Blood Sugar and O_2, ibid. **3**:49-58, 1940.

2. Knott, J. R., and Travis, L. E.: A Note on the Relationship Between Duration and Amplitude of Cortical Potentials, J. Psychol. **3**:169-172, 1936.

3. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **60**: 377-388, 1937; Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298-314 (Feb.) 1938. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: The Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, J. Neurol. & Psychiat. **1**:211-225, 1938.

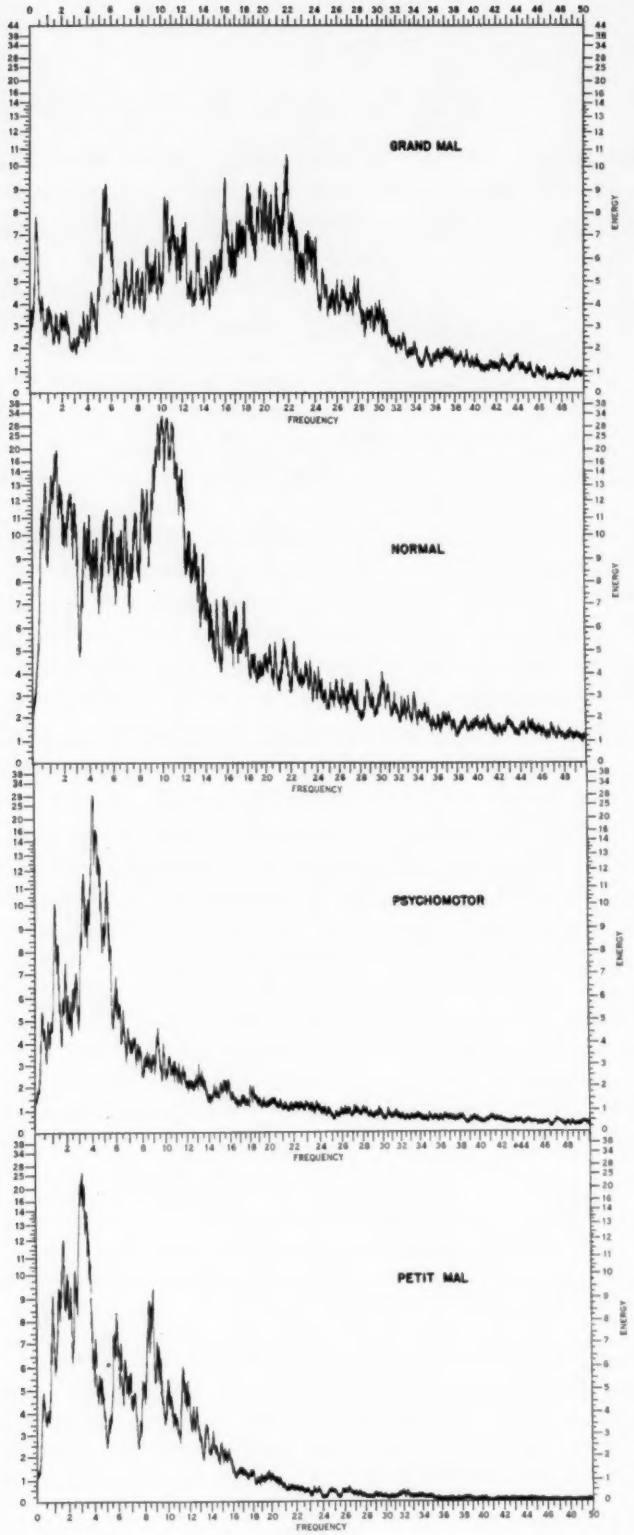

Figure 1

(See legend on opposite page)

and Drohocka [4] have recorded cortical activity with different filters in the system and have presented their data in the form of a spectrum.

In 1938, A. M. Grass developed a technic for obtaining a continuous spectrum from the electroencephalogram. By this technic, an irregular mixture of frequencies, such as appears in the electroencephalogram, is reduced to its Fourier transform. A description of the method has been published,[1b] but a summary will be given here for convenience. The electroencephalogram is recorded on film as a black and white profile, such as is generally used in sound recording. This type of record is called a shadowgram. A thirty second strip of film is made into a belt and rotated continuously between a light and a photoelectric cell. The resulting fluctuations in potential in the photoelectric cell are a reproduction of the electrical fluctuations obtained from the cortex. They are amplified and passed through an exceedingly sharp, continuously variable filter, the output of which is recorded with an ink-writing meter on coordinate paper. The range of frequencies included in the present study is from 1 to 50 per second.

In earlier reports [3] based on inspection of ink records, we have said that cortical activity becomes too fast in grand mal attacks, too slow in psychomotor seizures and alternates between too fast and too slow in petit mal attacks. When the activity recorded during the first part of each of these types of seizures is reduced to a spectrum, it appears that in grand mal attacks an abnormally great proportion of energy is indeed found at the fast end of the spectrum (figs. 1 and 2) and in psychomotor seizures an abnormally great proportion of energy is found at the slow end of the spectrum. Analysis reveals, however, that in petit mal attacks the major energy discharge is even slower than in psychomotor seizures. There is so much more energy in the 3 per second rhythm of petit mal than in the faster component, the spike, that the energy in the faster component appears insignificant. We have described the petit mal seizure discharge as containing a fast component such that if repeated to form a continuous pattern it would have a frequency of from 15 to 20 per second. It does not repeat to form a true frequency, however; it is present only one twentieth of the time. One would not expect

4. Drohocki, Z., and Drohocka, J.: L'électrospectrogramme du cerveau, Compt. rend. Soc. de biol. **130**:95-98, 1939.

EXPLANATION OF FIGURE 1

Fig. 1.—Spectrums from the left motor area during three types of seizures, compared with a typical normal spectrum. Each spectrum was obtained from a different patient, but an epileptic person may show at different times any of these types of energy distribution.

to find much energy in the 15 to 20 per second band, even though the spike has a high amplitude. If the spike component is considered by itself, it is apparent that since the spikes repeat every third of a second, they form asymmetric square waves with a frequency of 3 per second, which adds to the energy in the 3 per second band. It is the 3 per second peak, therefore, which dominates the spectrum of petit mal. The asymmetry of the 3 per second waves introduces strong harmonics which appear in the 6, 9 and 12 per second positions.

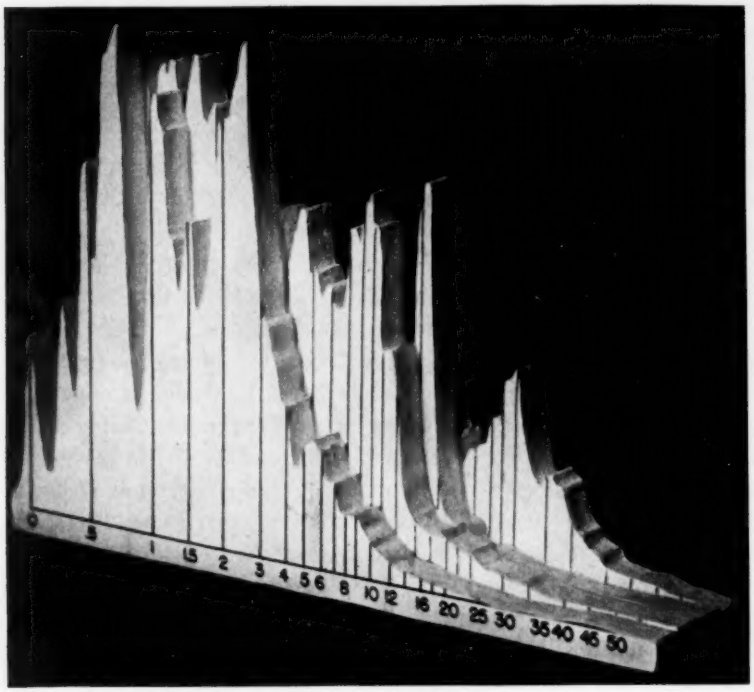

Fig. 2.—Cut-outs of spectrums from the left motor area during three types of seizures, compared with a typical normal spectrum. The order is the same as in figure 1, the petit mal spectrum being in front and the grand mal spectrum in back. A later stage of a psychomotor seizure is shown, in which the maximum energy appears at a frequency of approximately 7 per second, instead of 4 per second, as in figure 1. The patient was confused but responsive. A logarithmic, instead of the usual linear, scale is used for frequency in this figure.

Cortical spectrums were obtained on a patient who had several tonic-clonic convulsions a day. As the seizure developed, there was a shift in the distribution of energy toward the fast side of the spectrum. This continued until consciousness was lost. Coincident with a further shift to the fast side, the tonic phase of the seizure started, and as the

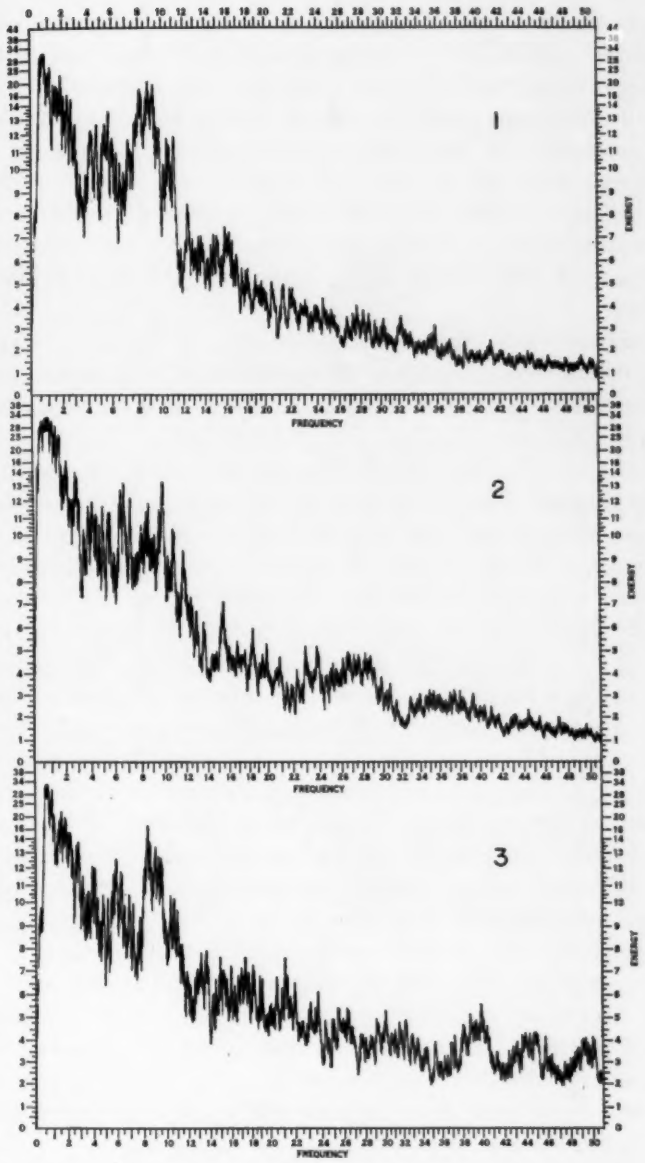

Fig. 3.—Shifts in the cortical spectrum of an epileptic patient in the days preceding a seizure. The spectrums shown are from the right frontal area; they were taken on successive days and are part of a long series of daily spectrums obtained on this patient, who had grand mal seizures at approximately monthly intervals. On the day after spectrum 3 was obtained, the patient had a severe tonic-clonic convulsion.

postseizure stupor supervened, an abnormally great amount of energy appeared at the slow end of the spectrum.

When the spectrum of a patient with typical but rare grand mal seizures was studied on successive days, it was found that as the day of the seizures approached, more and more energy appeared at the fast end of the spectrum. After the seizure energy shifted to the slow end of the spectrum. On succeeding days it gradually assumed a normal distribution. Thus the patient with rare seizures showed fluctuations in the cortical frequency spectrum similar to those shown by the patient with frequent seizures, but in the former the cortical spectrum went through a cycle every twenty days; in the latter this cycle required only a few hours.

When spectrums from a normal subject on successive days were studied, it was found that there were gradual shifts in energy from day to day, but these were by no means as extreme as those which occurred in epileptic patients.

Records taken during seizure-free periods on 20 unselected adult epileptic patients were analyzed with the Grass analyzer in order to determine whether any characteristic shift in the spectrum is evident in epileptic persons as a class. A group of 20 normal adults has been studied and previously reported on.[5] In both epileptic and normal subjects, although certain differences tend to occur in spectrums from different cortical areas, a single definite abnormality tends to pervade the spectrums from all cortical areas. In epileptic persons an excessive amount of energy is found in the frequencies below 9 per second, and the normal 9 to 11 per second peak tends to be replaced by a peak in the 7 to 8.5 per second position. Since this abnormality is usually evident in all cortical spectrums, one average spectrum serves to illustrate it as well as another. In figure 4, the average right occipital spectrum of 20 normal subjects is compared with the average right occipital spectrum of 20 epileptic patients.

Although epileptic subjects tend in their interseizure periods to have certain abnormalities in common, they tend also to show certain abnormalities which are characteristic of particular seizure patterns. Six of the 20 patients in this series had only grand mal seizures. If these 6 patients are considered as a separate group, the average spectrum for the left motor area shows an abnormally great amount of energy at 24 and 29 per second. Five patients in the series had only psychomotor seizures. When these are considered as a separate group, no excess of energy appears in the fast frequencies, but instead an abnormally high peak in the 6 per second region.

5. Gibbs, F. A.: Cortical Frequency Spectra of Normal Adults, J. Nerv. & Ment. Dis., to be published.

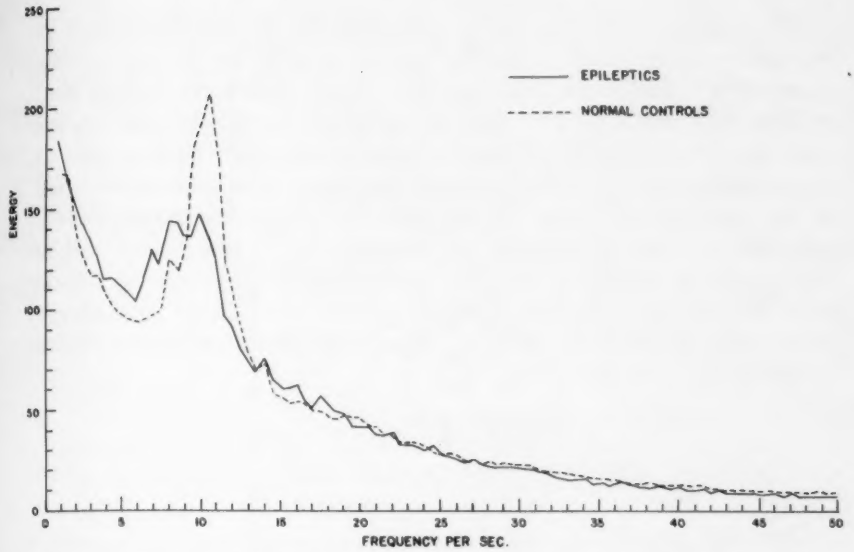

Fig. 4.—Average right occipital spectrum for 20 adult epileptic patients in their interseizure periods, compared with the average right occipital spectrum for 20 normal adults. Averages were obtained as follows: All right occipital spectrums were given the same area, i. e., amplified so that the total energy in each spectrum was the same. The energy at 1 per second in the 20 cases was added and divided by 20; similar computations were made for all frequencies and half-frequencies from 1.5 to 50 per second. The 100 values thus obtained were plotted to give the curves shown.

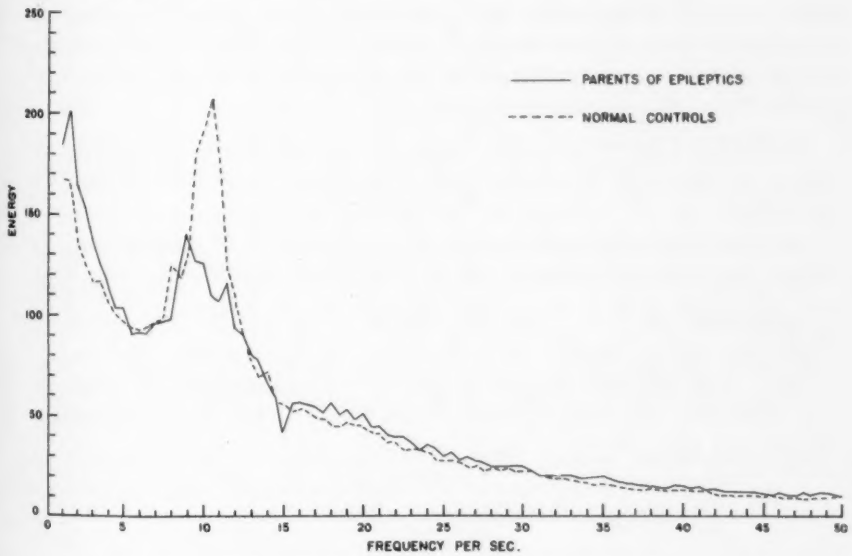

Fig. 5.—Average right occipital spectrum for 20 unselected parents of epileptic patients, compared with the average right occipital spectrum for 20 normal adults. Averages were obtained in the same way as those shown in figure 4.

Some normal subjects have spectrums like those encountered in epileptic patients. Such a finding was to be expected in view of our observation [6] that more than one half of the apparently normal near relatives of epileptic persons show dysrhythmia. In figure 5, the average right occipital spectrum of 20 unselected parents of epileptic persons is compared with the average normal spectrum. The average spectrum of the parents has some of the abnormalities characteristic of the spectrum of epileptic subjects, for although the 9.5 per second peak is higher than its neighbors, it is only slightly higher than the 8 per second peak. The average spectrum of the parents, however, shows more energy in the range between 15 and 30 per second than that of either the normal or the epileptic subjects.

SUMMARY AND CONCLUSION

The Grass method of frequency analysis has been used to obtain the cortical frequency spectrums of epileptic patients, of the parents of epileptic patients and of normal persons.

1. Study of records made during seizures discloses the following (*a*) In petit mal attacks a disproportionately high peak appears in the 2 to 3 per second region; (*b*) in a psychomotor seizure an abnormally high peak appears in the 4 to 7 per second region, and (*c*) in grand mal attacks an abnormally high peak is evident in the 20 to 29 per second region.

2. The average spectrum of epileptic patients made in the intervals between seizures disclose a disproportionately large amount of energy at frequencies below 9 per second. However, the subgroup of patients subject only to grand mal have an abnormally great amount of energy in the 20 to 29 per second region.

3. Patients having periodic grand mal attacks show an increase in energy in the faster frequencies as the day or the hour of the convulsion approaches.

4. The average spectrums of a group of parents of epileptic patients show abnormalities similar to those seen in the average spectrums of epileptic patients, but these abnormalities are less extreme.

6. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: The Inheritance of Epilepsy as Revealed by the Electroencephalograph, J. A. M. A. **113**:1002-1003 (Sept. 9) 1939; Inheritance of Cerebral Dysrhythmia and Epilepsy, Arch. Neurol. & Psychiat. **44**:1155-1183 (Dec.) 1940.

CUTANEOUS PRESSURE-VIBRATION SPOTS AND THEIR UNDERLYING TISSUES

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The purpose of this investigation has been to determine the sense receptors of pressure and vibration by means of cutaneous excision. The receptors involved in the mediation of pressure sensitivity have long been subject to speculation. The nature of the processes underlying the perception of vibration has been the subject of controversy for the last four decades. Vibration sense has been variously considered as mediated by the bones and periosteum and as a function of the tactual end organs responsible for "contact" and "pressure" sensibility, and some writers have even included a special "vibratory sense" as the sensory mechanism responsible for the perception of this modality. A summary of the work on vibratory sensibility is largely history of this controversy and has been presented in a recent review by Geldard.[1] Of the several views as to the nature of vibratory sensitivity growing out of the studies of physiologists, psychologists and clinicians, the results of recent investigations by Fessard,[2] Geldard,[3] Gilmer,[4] Piéron[5] and Weitz[6] have concurred with the early opinions expressed by Forli

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1. Geldard, F. A.: The Perception of Mechanical Vibration: I. History of a Controversy, J. Gen. Psychol. **22**:243-269, 1940.

2. Fessard, A.: Sur la loi de variation des temps de latence en fonction de l'intensité d'excitation, pour les sensations tactiles, Compt. rend. Soc. de biol. **104**: 1252-1254, 1930.

3. Geldard, F. A.: The Perception of Mechanical Vibration: II. The Response of Pressure Receptors, J. Gen. Psychol. **22**:271-280, 1940; The Perception of Mechanical Vibration: III. The Frequency Function, ibid. **22**:281-289, 1940; The Perception of Mechanical Vibration: IV. Is There a Separate "Vibratory Sense"? ibid. **22**:291-308, 1940.

4. Gilmer, B. von H.: The Relation of Vibratory Sensitivity to Pressure, J. Exper. Psychol. **21**:456-463, 1937.

5. Piéron, H.: Recherches expérimentales sur la sensation vibratoire cutanée, Ann. psychol. **36**:82-102, 1936.

6. Weitz, J.: Vibratory Sensitivity as Affected by Local Anesthesia, J. Exper. Psychol. **25**:48-64, 1939.

and Barrovecchio,[7] Ballien,[8] Treitel[9] and von Frey[10] that cutaneous vibratory sensibility is but another temporal expression of pressure.

The history of our present problem is to be found in the attempts that have been made to establish correlations between the various cutaneous sensory qualities of pressure, pain, cold and warmth and their possible receptors. However, these relations have never been convincingly shown. Von Frey has often been credited with establishing such relations, but, as has been pointed out by Dallenbach,[11] he was duly cautious and conservative in stating his theory. Von Frey based his correlations on the observations that end organs which he associated with different cutaneous sensory qualities were found in places at which those qualities are especially prominent or exclusively present. Dallenbach[11a] in 1927 (page 427) pointed out:

> The further we get away from von Frey the more dogmatic in general become the statements regarding his correlation. The writers of textbooks during the first decade following the formulation of the theory were reserved in their statements concerning it; in the next decade they were less so; and during the past decade the writers have very frequently given the correlation as established fact.

However, some present day writers have been more cautious in stating the possible relations between the different cutaneous sensory qualities and specific sense receptors. But Ruffini cylinders are still considered by some as possible receptors of warmth, and Krause end bulbs are often said to be identified with cold spots. Hair receptors are thought of in connection with pressure sensitivity in hairy regions of the body. Meissner corpuscles are usually supposed to serve the pressure sense on the hairless portions of the skin. And free nerve fibers are often considered to be the cutaneous pain receptors. But it will take only a brief review of the literature to show that both the "direct" and the "indirect" cutaneous excision experiments[12] have not com-

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7. Forli, V., and Barrovecchio, B.: Ein weiterer Beitrag zur Kenntnis des Vibrationsgefühls, Med. Klin. **1**:851-853, 1905.

8. Ballien, M.: Klinische Beiträge zur Kenntnis der Vibrationsempfindung, Thesis, Greifswald, Merseburg, Rössner, 1906, p. 31.

9. Treitel, L.: Das Vibrationsgefühl der Haut, Arch. f. Psychiat. **40**:419-421, 1905.

10. von Frey, M.: Physiologische Versuche über das Vibrationsgefühl, Ztschr. f. Biol. **65**:417-427, 1915.

11. Dallenbach, K. M.: (*a*) The Temperature Spots and End Organs, Am. J. Psychol. **39**:402-427, 1927; (*b*) A Bibliography of the Attempts to Identify the Functional End Organs of Cold and Warmth, ibid. **41**:344, 1929.

12. The term "direct" excision experiment is used here to describe the removal and the histologic analysis of cutaneous tissue directly underlying a specific area

pletely supported these contentions. However, the results of some of the investigations, inconclusive in themselves, may be of significance when interpreted in the light of the present report.

The first direct excision experiment was performed in 1885 by Donaldson,[13] when he examined histologically the tissue underlying cold and warm spots. The results of this investigation were interpreted as "negative," since no specialized end organs were found. The numerous nerves found beneath these spots were disregarded, since the nerves were almost as numerous in neighboring parts of the tissue.

Goldscheider,[14] in 1886, carefully marked warm, cold and pressure spots on his left forearm, excised the tissue containing these spots and examined it histologically. He found no corpuscular nerve endings but observed different forms of arborized nerve tissue. He found it difficult to distinguish anatomically between the nerve terminations corresponding to the warm and those to the cold spots, but concluded that the plexuses underlay a temperature sense and had a specific relation to blood vessels.

Häggqvist,[15] in 1913, reported observing smooth muscle bundles under cold spots. Stetson,[16] in a series of experiments in 1923, reported on the relation existing between the hair follicle and the sense of pressure. These investigations were made with the hairs on the scrotum, and from them he concluded that pressure sensation in this hairy region is mediated by the upper part of the follicle, and possibly by the surface of the skin at the point of emergence of the hair. In mediating pressure sensation the hair acts as a lever of a second order by compressing the upper part of the follicle, which is richly surrounded by nerve terminations. Deformation of the surface of the skin near the point at which the hair emerges also can excite these endings. Stetson concluded that the hair follicle is not furnished with endings for pain sensation.

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of the skin, or sensory "spot." An "indirect" excision experiment is one including a histologic analysis of comparatively large areas of the skin taken from a surgical specimen without predetermining precise sensory "spots," or the analysis of rather large areas of the skin containing a number of known sensory "spots" without an attempt to correlate specifically a given sensory "spot" with the tissue directly underlying it.

13. Donaldson, H. H.: On the Temperature Sense, Mind **10**:399-416, 1885.

14. Goldscheider, A.: Histologische Untersuchungen über die Endigungsweise der Hautsinnesnerves beim Menschen, Arch. f. Anat. u. Physiol., Physiol. Abtheil., supp., 1886, pp. 191-227.

15. Häggqvist, G.: Histophysiologische Studien über die Temperatursinne der Haut des Menschen, Anat. Anz. **45**:46-63, 1913.

16. Stetson, R. H.: The Hair Follicle and the Sense of Pressure, in Psychological Monographs, Princeton, N. J., The Psychological Review, 1923, vol. 32, no. 3, pp. 1-17.

In 1925 Strughold and Karbe [17] noted a relation between cold spots and Krause end bulbs in the conjunctiva of the eye. However, it is questionable whether one can apply this correlation in dealing with the external skin.

In 1927 Dallenbach [11a] found in serial sections taken from his excisions of cold and warm spots only free nerve endings and concluded that these, besides functioning in pain sensibility, also subserve the functions that von Frey ascribed to Krause end bulbs and Ruffini cylinders. Pendleton,[18] one year later, made biopsies of cold spots but reported that no specific end organ was found. He pointed out the possibility that enough tissue was not removed. The biopsy incisions were made by means of a 2 mm. dermic punch, with the depth of the incision varying from just below the epidermis to (probably) the full depth of the corium. Stimulation of the cold spots after the biopsy wound had healed showed a return of cold sensibility, at the edge of the incision, after some time (about sixty days).

Waterston,[19] in 1933, explored the terminal parts of the fingers for touch, pain and temperature sensation. The epidermis was then removed by slicing. Only touch, not pain, was sensed by this removal. The removed portions of the epidermis were examined histologically. Fine nerve fibers were found terminating in the epidermis in "loops and figures." Waterston concluded (page 256): [19]

> This demonstration of the presence of nerve fibers and of their terminals in the tissue which had been removed, without causing any pain, completes the evidence necessary to establish the theory which I have put forward, viz., that the nerves of the epithelium are the nerves of light tactile sensation, and that they do not under ordinary conditions convey the impulses which give rise to pain. . .
>
> If the evidence now obtained of this theory be accepted it will be necessary to abandon two views which are widely quoted, viz., that nerve fibers of epithelium subserve the sensation of pain, and that the Pacinian bodies or Meissner corpuscles are the receptors for light touch. Both of these theories are now untenable and other functions must be sought for these and other similar organs of the corium.
>
> Sensibility to superficial pain on the other hand is subserved by the corium. With the twofold structure of the skin, epidermis and dermis, there is a division of sensory function, the epidermis the organ of touch, the corium that of superficial pain.

Waterston expressed the opinion that pressure is not a cutaneous sensation, but is elicited on the surface of the skin if stimulation is sufficiently strong to affect deeper tissues, such as the muscle or the periosteum.

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17. Strughold, H., and Karbe, M.: Vitale Färbung des Auges und experimentelle Untersuchung der gefärbten Nervenelemente, Ztschr. f. Biol. **83**:297-308, 1925.

18. Pendleton, C. R.: The Cold Receptor, Am. J. Psychol. **40**:353-371, 1928.

19. Waterston, D.: Observations on Sensation: The Sensory Functions of the Skin for Touch and Pain, J. Physiol. **77**:251-257, 1933.

The possible organs of temperature sensations were not revealed by this excision work.

In a brief account of an excision experiment on cold spots, reported in 1933, Belonoschkin [20] attributed to a nonencapsulated ending, situated 0.1 to 2 mm. below the epidermis, the mediation of cold sensations. The excisions were made on the mammary gland. These endings are similar to those reported by Woollard [21] two years later. Woollard, working on the skin on the volar surface of the forearm, found immediately in the vicinity of the cold spots a complicated nerve plexus lying subjacent to the epithelium and just above the loops of the capillaries. This plexus consists of fibers of moderate thickness which branch and subdivide in a diffuse manner. The terminations are in the form of expansions of considerable size, sometimes elongated and sometimes ovoid. The ends are nonencapsulated, though they lie close enough together to give the impression of a well localized ending.

The experiments of Woollard differed from the previous excision work in that he removed successive slices of the epidermis and the dermis as far as the subcutaneous fat, periodically stimulating the spot with cold. Woollard stated (page 366): [21]

> So long as the ending is present its special receptor quality can be elicited . . . A fragment of the ending can still exhibit the special receptor quality . . . The special quality may be annulled immediately after section of the skin (cold), but if the ending is still present its quality returns after a time . . . When the ending is cut away the nerve fibre cannot be aroused by the original stimulus, even when this is intensified.

In the same group of experiments, Woollard found fine beaded fibers traveling into the epidermis beneath pain spots. These fibers seem to be the same as those attributed by Waterston [19] to touch. However, Woollard stated that touch is a function of the fibers encircling hair follicles, and concluded (page 367): [21]

> In general it may be put forward that pain, cold and touch have characteristic positions, fibres and ends.

On the whole, therefore, the results of these direct excision experiments may be considered as inconclusive. Likewise, the indirect excision work affords little in the way of solving the problems of cutaneous receptors, as is shown by the two typical investigations to be cited now.

Gilbert, in 1929,[22] using samples of human skin taken from the thigh, abdomen, breast, chest and leg and the middle of the sole of the

20. Belonoschkin, B.: Ueber die Kaltrezeptoren der Haut, Ztschr. f. Biol. **93**: 487, 1933.

21. Woollard, H. H.: Observations on the Terminations of Cutaneous Nerves, Brain **58**:352-367, 1935.

22. Gilbert, R. W.: Dermal Sensitivity and the Differentiated Nerve Terminations of the Human Skin, J. Gen. Psychol. **2**:445-461, 1929.

foot, made histologic examinations of the tissue. From the distribution of various end organs found in these regions, as compared with the known sensitivity of the skin of these areas, he concluded that Meissner corpuscles and hair follicles may be the end organs for superficial light pressure or touch sensitivity, but that the dearth of Krause end bulbs in some of the hairy regions makes it impossible to believe that they function for cold. Likewise, he concluded that the Ruffini ending is not a specific warmth receptor.

In 1932 Bazett, McGlone, Williams and Lufkin [23] described the various sensory end organs demonstrable in the prepuce and their possible correspondence to warm, cold and touch sensations found in this region. They inferred that sensation of touch may be accounted for by atypical nonencapsulated end bulbs, made up of very fine, richly anastomosing branches. They maintained that Meissner corpuscles cannot be responsible for light touch sensation in the prepuce, although they may well account for sensations produced by more extensive deformation of the skin. Meissner corpuscles are found in prepuce material at a considerable depth, and then only one or two are present per square centimeter. They concluded that there can be little doubt of the correctness of the orthodox view that free nerve endings subserve pain sensation.

LOCALIZATION AND EXCISION OF THE SENSORY AREAS

A detailed account of the apparatus used and the methods employed in localizing the pressure-vibration–sensitive spots has been described in an earlier publication by one of us (B. V. H. G.).[4] Two methods of approach have been followed. One has involved the use of alternating electric currents generated by a beat frequency oscillator, amplified through two stages and applied to the surface of the skin by a small needle electrode. The apparatus was provided with a voltameter and milliammeter for measuring sensory thresholds in terms of power. The second approach made use of a mechanically vibrated needle, driven by the amplified current from a beat frequency oscillator. Thresholds were measured in terms of amplitude swing of the needle. The mechanical transmission of vibratory "waves" in the skin was observed stroboscopically through the use of a procedure described by Weitz [6] and by Geldard.[8] In exploring the skin for the vibration-sensitive spots, a frequency of 100 cycles was arbitrarily used. However, before excisions were made, the frequency range for each sensitive area was determined.

Through the use of the alternating electric currents applied to the surface of the skin by a small needle electrode, one can localize pressure-vibration spots with accuracy. Exploring the skin for pressure-vibration spots in this manner offers

23. Bazett, H. C.; McGlone, B.; Williams, R. G., and Lufkin, H. M.: Sensation: I. Depth, Distribution and Probable Identification in the Prepuce of Sensory End Organs Concerned in Sensations of Temperature and Touch; Thermometric Conductivity, Arch. Neurol. & Psychiat. **27**:489-517 (March) 1932.

certain advantages over trying to localize pressure spots by the use of hairs or other conventional esthesiometers. Since, when applied to the surface of the skin, the electrical stimulations elicit either various patterns of pain associated with vibration sensation or of vibration sensation free from pain, one can easily "tune in" the pressure-vibration spots.

Vibration sensations are here defined as those giving only clear perceptions of interrupted pressure, the vibratory "pattern" being entirely free from all pain experience.

After the pressure-vibration spots had been located through the use of the alternating electric current, their sensitivity to mechanical vibration was investigated. Later these spots were tested for pressure sensitivity by the use of a hair esthesiometer. In general, the latter procedure confirmed the localizations obtained by the electrical stimulations. After the pressure-vibration–sensitive spots were located, they were marked by injecting ink near the spot. The sensitivity of each spot was checked periodically over a period of weeks. The spots were found to remain stable in position, and they yielded virtually the same vibratory thresholds from day to day. Before the excisions were made each spot was tested for temperature sensitivity through the use of specially prepared temperature cylinders.

Nine direct excisions were made in our investigation, the biopsy specimens being removed from 2 subjects who were well trained in the observation of cutaneous sensitivity. The excisions were made from regions of the back and arms, these areas of skin being selected because of the "relative isolation" of the sensitivity. Of these 9 areas selected for biopsy 3 showed only pressure-vibration sensitivity, 2 were highly sensitive to cold stimulation, in addition to having pressure-vibration sensitivity, and 2 were sensitive to heat along with sensitivity to pressure and vibration. The 2 remaining biopsy specimens were taken as controls. We were unable to find areas of skin large enough for adequate excision that were completely free of sensitivity to pressure, vibration and temperature. Therefore, our control biopsy specimens contained tissues which were relatively insensitive to mechanical vibration, pressure and temperature stimulations and which transmitted primarily feelings of pain in response to the electrical stimulation.

The excisions, of areas 2 to 3 mm. in diameter in some instances, were made with a scalpel.[24]

In each biopsy specimen the pressure-vibration–sensitive "stimulus point" was localized near the center of the surface area. The cutaneous tissue was removed in the form of a cone, the specimens ranging in depth from about 2 to 6 mm. The deeper excisions went well below the dermal level into the subcutaneous fatty tissue. The more shallow excisions went only through the dermal layer of the skin. Each biopsy specimen was removed with local anesthesia induced with procaine hydrochloride, the anesthetization having no effect on the histologic technics used. Immediately on removal, the excised tissue was placed in a fixing solution.

TECHNICAL PROCEDURES

The most difficult phase of the study was to find a reliable method for staining sensory nerve endings and differentiating neuraxons and nerve fibers from reticulum and elastic tissue. The first 2 biopsy specimens were fixed in a dilute neutral

24. Dr. Joseph Soffel, of the West Penn Hospital, Pittsburgh, rendered surgical service in this study.

solution of formaldehyde U. S. P. (1:10) and the third in Bouin's fluid.[25a] Neither of these fixatives were satisfactory for differentiating nerve tissues, since the sections stained with silver were not uniform in their reactions.

Several Golgi preparations were available for comparison, but, owing to the scarcity and almost prohibitive cost of osmic acid, a less expensive method was desired. It was decided to take punch specimens from autopsy material and amputated extremities and to try various fixatives and methods. Many fixatives were tested, including Zenker's stock fluid,[25b] with and without glacial acetic acid, Zenker's fluid in which phosphomolybdic acid was substituted for glacial acetic acid, Helly's fluid,[25c] Cajal's uranium nitrate method [25d] for nerve cells and modified Cajal fixatives in which cobalt or nickel was substituted for uranium. Weigert's fixative and mordant for medullated nerves [25e] also were used. The fixative of choice varied with the staining method to be used. The later biopsy specimens were fixed in Cajal's uranium nitrate fluid B for nerve cells.

After fixation each of the biopsy specimens was embedded in paraffin, sectioned serially and mounted on slides by means of Masson's gelatin [25f] so that each slide held from six to twenty sections.

No single stain was found that brought out all of the nerve elements which we desired to study. One or more slides from each biopsy specimen were prepared with Mallory's phloxine–methylene blue (methylthionine chloride) stain,[25g] Masson's trichrome stain,[25h] Wilder's modification of Bielschowsky's silver stain,[25i] and Bodian's [25j] silver stain. Various counterstains, including Van Gieson's stain [25j] and Mallory's phosphotungstic acid hematoxylin,[25k] were used with the silver methods. The best results in our hands were obtained with tissue fixed in Zenker's fluid and stained by Wilder's silver method, followed by differentiation according to Pal and overnight counterstaining with Mallory's phosphotungstic acid hematoxylin, and with tissues fixed and stained in Cajal's uranium nitrate fluid by Bodian's silver method and counterstained with Mallory's phosphotungstic acid hematoxylin, the potassium permanganate–oxalic acid procedures being omitted. Ransom's [25m] and Popoff's [26] technics were disappointing in our experience. Weigert's myelin sheath method appeared to bring out medullated nerve filaments, elastic fibers and sometimes nerve end plates. It had the disadvantage of being applicable to blocks of tissue rather than individual sections. The glomus bodies and the Meissner corpuscles were best differentiated by Masson's trichrome stain, although some one of the silver methods had to be used in order to see the nerve supply of the Sucquet-Hoyer canals.

RESULTS OF BIOPSIES

In contrast to the evidence in reports of researches reviewed in the earlier part of this paper, most of the textbooks of histology assign

25. Mallory, F. B.: Pathologic Technique, Philadelphia, W. B. Saunders Company, 1938: (*a*) Bouin's Fluid, p. 45; (*b*) Zenker's Fluid, p. 43; (*c*) Helly's Fluid, p. 44; (*d*) Cajal's Uranium Nitrate Fixative—Solution B, p. 115; (*e*) Weigert's Fixative and Mordant for Medullated Nerves, p. 231; (*f*) Masson's Gelatin, p. 58; (*g*) Mallory's Phloxine-Methylene Blue, pp. 86-87; (*h*) Masson's Trichrome Stain, p. 156; (*i*) Wilder's Modification of Bielschowsky's, p. 163; (*j*) Van Gieson's Stain, p. 152; (*k*) Mallory's Phosphotungstic-Acid-Hematoxylin Stain, p. 241; (*l*) Bodian's Stain, p. 228; (*m*) Ransom's Stain, p. 224.

26. Popoff, N. W.: The Digital Vascular System, Arch. Path. **18**:295-330 (Sept.) 1934.

sensory impulses to specific receptors with considerable assurance. For example, the sensations of touch are attributed to nonmedullated fibers and to Merkel-Ranvier corpuscles in the malpighian layer and to Meissner corpuscles in the papillae of the corium. The perceptions of pain, heat and cold are usually attributed to free nerve filaments in the corium and to Krause end bulbs or to the Golgi-Mazzoni corpuscles in the areas in which they are situated. According to Bailey,[27] the Krause corpuscles are not generally distributed, but are found in the conjunctiva, the mucous membranes of the cheeks and nose, the skin of the external genitalia and various deep-situated structures. Cowdry [28] showed a diagram taken from Starling's "Physiology" which raised the question of the assignment of deep pressure to the Vater-Pacini corpuscles. Ordinary pressure and vibration sensitivity in the skin seems to have been left to future observations.

In order that each biopsy specimen should be examined thoroughly, a routine search of each section was made layer by layer for the following structures:

The malpighian layer was studied for free filaments of nonmedullated nerve fibers, for filaments ending in the tactile disks of Merkel and Ranvier and for the argentophil Langerhans cells, since these cells have sometimes been considered among the sensory nerve end organs.

The corium was searched for arborized terminal branches of networks of nonmedullated fibers, especially for those immediately beneath the malpighian layer, for end brushes of Ruffini, for angular swellings of the filaments, for endings in and on the vascular walls, for independent glomeruli in the connective tissues and for the encapsulated end organs, including Meissner's corpuscles, Ruffini's cylinders, Krause's end bulbs and the end bulbs of Pacini.

Perivascular arborizations were traced from section to section. Their networks and disklike endings were sought in and about arterioles, capillaries and venules.

All sections were examined for arterioles of the glomus type and for portions of Sucquet-Hoyer canals, which often lead upward from the more deeply seated glomus bodies of Masson.

Hair follicles, sebaceous glands, sweat glands and arrector pili muscles were carefully examined with reference to their nerve supplies.

Finally, myelinated nerve bundles were followed for divisions and their relation to other structures.

Biopsy 1.—*Sensitivity.*—The area of excision was located near the middle of the back. It was sensitive to pressure and mechanical vibration. Feelings of

27. Bailey, F. R.: Textbook of Histology, ed. 9, Baltimore, William Wood & Company, pp. 277, 279, 280 and 282.

28. Cowdry, E. V.: A Textbook of Histology, Philadelphia, Lea & Febiger, 1934, p. 337.

vibration were elicited by the alternating electric current. The area was relatively insensitive to temperature stimulation.

Histologic Structure.—The stratum Malpighii showed a considerable number of argentophil cells, some of which were crescent shaped and resembled Merkel-Ranvier endings save that no nonmedullated fibers were found leading to them. Free, nonmedullated plexuses were observed just beneath the malpighian layer, and these appeared to be continuous with the plexuses about the capillary walls. Perivascular plexuses were abundant. They were difficult to differentiate from the reticulum, although many more stained with Wilder's than with Bodian's stain. An occasional nonmedullated fiber ending in a small plate in the capillary wall was noted. The perivascular plexuses were abundantly arranged about arterioles, capillaries and venules and appeared to be the chief channels for the passage of the nerve fibers through the corium to the malpighian layer. Among the vessels was an arteriole having several layers of cubical smooth muscle cells and no internal elastic membrane. This was believed to be an armlike extension from a glomus body. The biopsy specimen contained one hair follicle with sebaceous glands and two arrector pili muscles. A sweat gland duct occurred near the center of the section. Serial sections failed to show Meissner corpuscles, Krause end bulbs or pacinian corpuscles. A medullated nerve was seen to divide and connect with a plexus about an arteriole.

Biopsy 2.—*Sensitivity.*—The area of excision was located on the left side of the back near the belt line. It was sensitive to pressure and mechanical vibration. Feelings of vibration were best elicited by the alternating electric current. The area was relatively insensitive to temperature stimulation.

Histologic Structure.—The section was fixed in Bouin's fluid. In the center of the biopsy specimen was a miliary abscess which extended almost entirely through the malpighian layer. It was covered with a fibrinous crust, in the meshes of which were many leukocytes.

The malpighian layer contained many argentophil, crescent-shaped Merkel-Ranvier cells. Nonmedullated fibers were not seen in the malpighian layer. The usual network of submalpighian, arborized fibers was present about the capillaries. In one of the deeper arterioles the arborization was unusually profuse. Nonmedullated fibers accompanied a sweat gland duct near the center of the section. No encapsulated sensory end organs of any kind were found.

No true glomus bodies were seen, although one of the vascular plexuses contained a structure resembling the cross section of an arteriovenous anastomosis.

The piece was devoid of hair follicles and sebaceous glands. It contained three sweat gland ducts that were widely separated and two bundles of arrector pili muscles. The most centrally located of the ducts emptied near the abscess and showed profuse infiltration with lymphocytes and plasma cells throughout its length. At the lowest tip of the specimen there was a small trunk of medullated nerves.

Biopsy 3.—*Sensitivity.*—The area of excision was located on the ventral surface of the left forearm midway between the wrist and the elbow. It was sensitive to pressure and mechanical vibration. Feelings of vibration were elicited by the alternating current at a point about 0.25 mm. from the spot most sensitive to pressure and mechanical vibration. The area was highly sensitive to cold.

Histologic Structure.—The malpighian area was covered with a thick cornified layer and contained the mouths of several sweat gland ducts. In parts of the

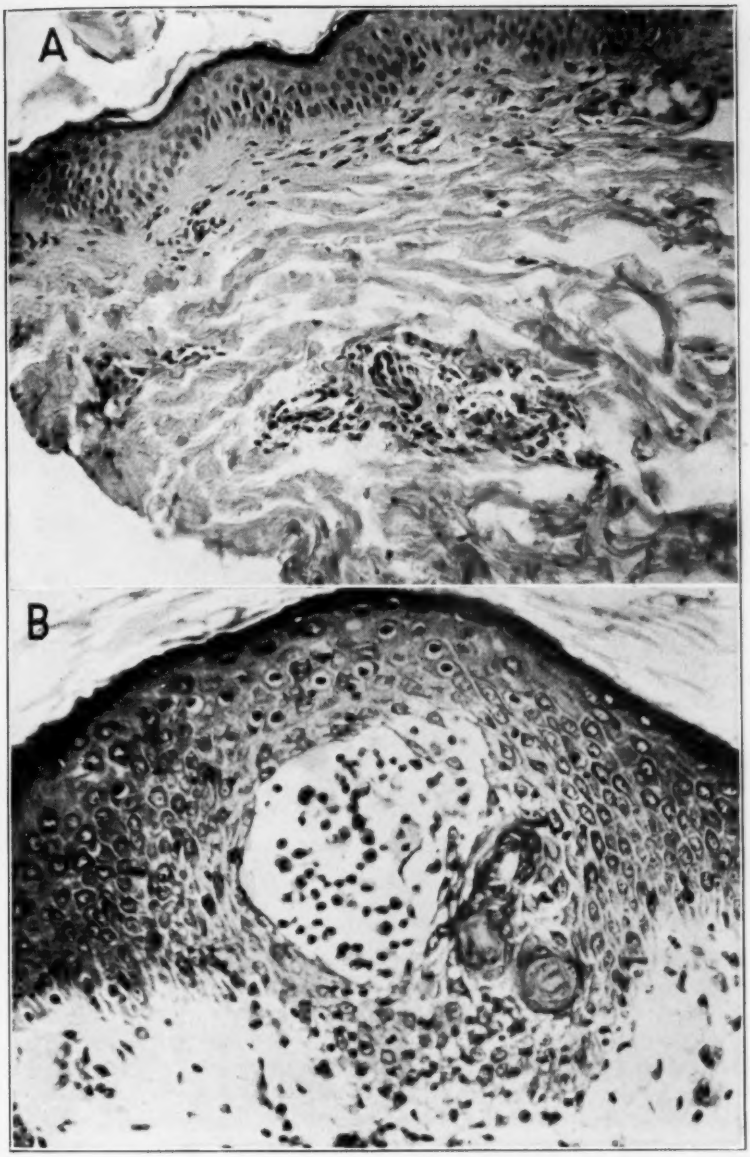

Fig. 1.—*A,* typical section from experimental biopsy specimen 1. The area was sensitive to pressure, mechanical vibration and vibration by alternating current and relatively insensitive to temperature stimulation. The biopsy specimen included the papillary and reticular zones and the superficial part of the subcutaneous zone. The group of vessels beneath the central zone was made up of small arterioles and veins, which were surrounded by a fine reticulum. In silver preparations of this block, both nerve fibers and collagenous reticular fibrils were seen. Magnification, 130.

B, section from experimental biopsy specimen 3. The area was sensitive to pressure and mechanical vibration and highly sensitive to cold. Note the miliary abscess in the malpighian layer near the sweat gland ducts. Magnification, 240.

sections stained by the Wilder–phosphotungstic acid hematoxylin method nonmedullated fibers were observed entering the malpighian layer. Crescent nuclei, with vacuoles around them, were accepted as Merkel corpuscles.

Silver-positive subcutaneous brushes of radiating fibers were seen extending upward through the papillae into the malpighian coat. These argentophil structures took the acid fuchsin when Masson's stain was used. One of the brushes occurred just at the end of a capillary at the tip of a papilla. Similar fibers followed the course of the capillary into the corium. No encapsulated end organ could be found either with Masson's stain or with any of the silver methods.

The perivascular arborizations were present. Several small loops having cubical or square muscle cell coats were suggestive of a Sucquet-Hoyer canal, save that they were not more than two layers thick. No pacinian corpuscle was found.

The biopsy specimen contained two hair follicles, a sebaceous gland, two arrector pili muscle bundles and several sweat gland ducts. It was not possible to differentiate nerve end plates. There was a coil of sweat glands at the bottom of the section, with a fairly large medullated nerve trunk and two loops of the muscle coils of a glomus body beside it.

Beginning with the eighth slide, there was a portion of a duct surrounded by an inflammatory exudate. At the exit of this duct in the malpighian layer was a small periductal abscess.

Biopsy 4 (control).—*Sensitivity.*—The area of excision was located near the middle of the back. It was relatively insensitive to pressure and mechanical vibration.

Stimulation by the alternating electric current induced a feeling of "stinging vibration" associated with pain. The observer reported the latter sensation to be of "diffused" nature. The area was relatively insensitive to temperature stimulation.

Histologic Structure.—The biopsy specimen was embedded at an angle, so that the first few sections were cut tangentially. The malpighian layer contained many fibers that took the silver stain. One fiber could be traced to a Merkel cell. There was a miliary abscess near the opening of the only sweat duct in the block, and above this was a crust of fibrin and leukocytes.

In the corium was a large arteriole of the ordinary type, with many branches spreading out beneath the malpighian coat and extending into the papillae. The argentophil reticulum about the vessels was heavily stained, and the nerve fibers could not be differentiated from the reticular fibrils in the silver preparations. A sweat gland duct led downward through the center of the biopsy specimen. No glomus bodies were found, and there were no encapsulated sensory end organs. Because of the tangential cutting of part of the block, Meissner end organs would have been easily seen if any had been present.

Biopsy 5.—*Sensitivity.*—The area of excision was located on the left side of the back about 10 inches (25.4 cm.) above the belt line. It was sensitive to pressure and mechanical stimulation. Feelings of vibration were elicited by the alternating electric current. The area was relatively insensitive to temperature stimulation.

Histologic Structure.—Near the center of the section was a portion of a hair follicle, at the side of which was a rich plexus of nonmedullated nerve fibers. Some of these extended for a very short distance into the malpighian layer. In the fourth section of the seventh slide a spray of these fibrils appeared to spread out and end freely among the epithelial cells. In the same section the attachment of the arrector pili muscle was seen in the hair follicle.

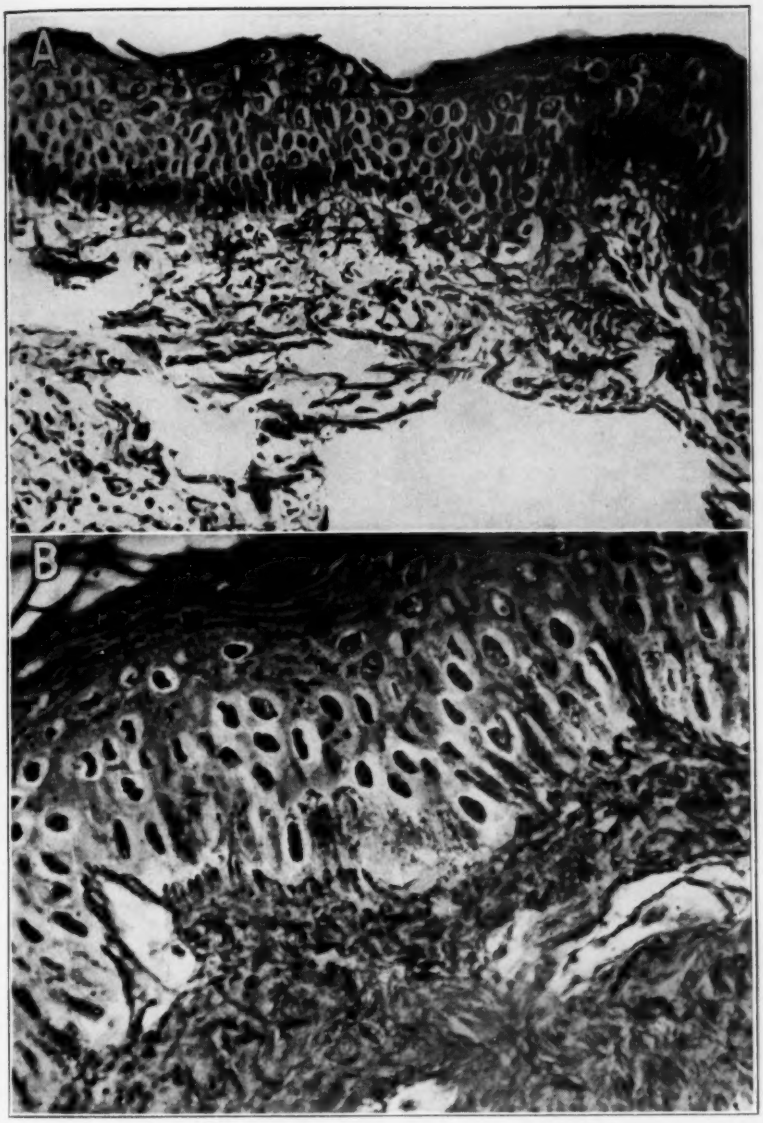

Fig. 2.—*A*, section from experimental biopsy specimen 8. The area was sensitive to pressure, mechanical vibration and vibration by alternating current and highly sensitive to heat. Note several Merkel-Ranvier corpuscles in the basal layer of the epithelium. The subepithelial zone contained argentophil fibers, among which were nonmedullated nerves. Wilder's silver stain, counterstained with Mallory's phosphotungstic acid hematoxylin; magnification, 180.

B, section from biopsy specimen 5. The area was sensitive to pressure, mechanical vibration and vibration by alternating current and relatively insensitive to temperature stimulation. Note two Merkel-Ranvier corpuscles in the basal layer and the profuse argentophil fibrils beneath the epithelial layer. At the right side of the section a nonmedullated nerve fiber can be seen entering the malpighian layer. Wilder's silver stain and Mallory's phosphotungstic acid hematoxylin; magnification, 480.

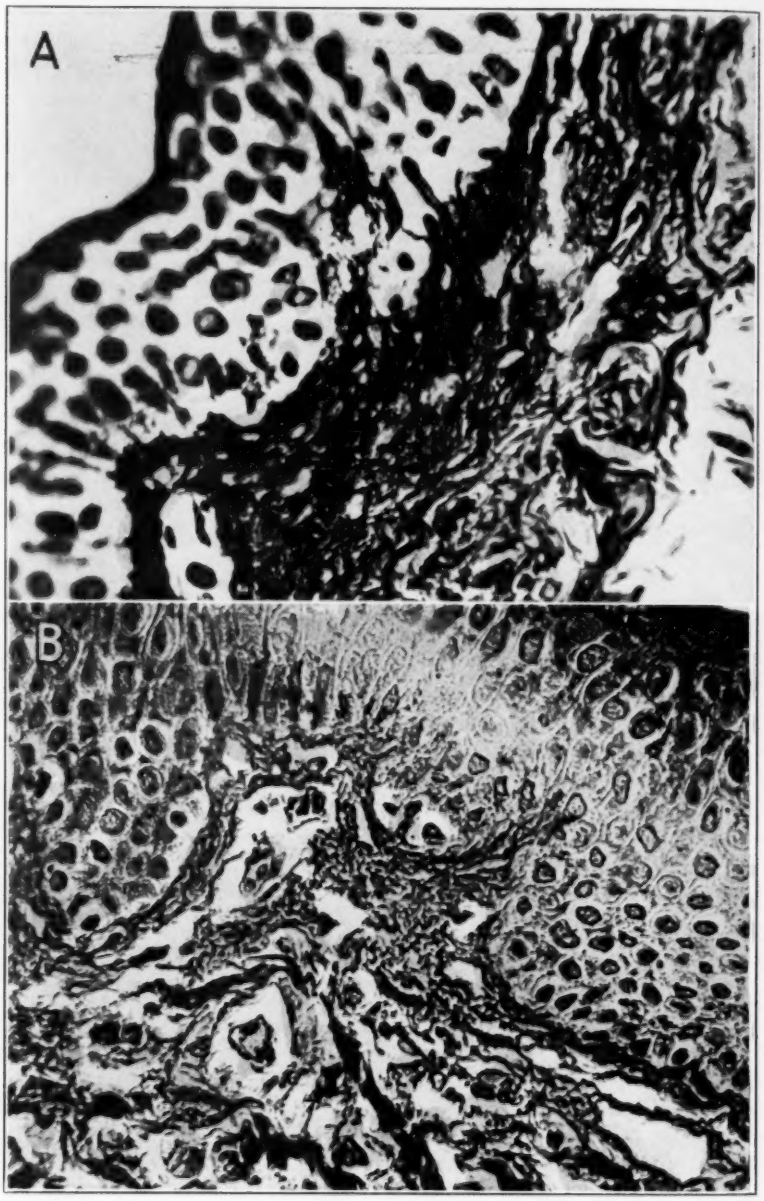

Figure 3

(See legend on opposite page)

Beneath the malpighian layer was a small group of vessels having a very rich nerve supply. Free filaments were spread out beneath the epithelium. At the side of one of the coils of vessels both medullated and nonmedullated nerves could be seen. No encapsulated end organs were found.

In the lower part of several serial sections there appeared to be a portion of a true glomus. It seemed to be connected directly by vascular extensions to the subepithelial capillary plexus, and the perivascular nerves and the arborized subepithelial nerves were intimately associated.

The piece contained one hair follicle, three sweat gland ducts and several small groups of arrector pili muscles.

At the side of the glomus there was a small bundle of myelinated nerves. Near the hair shaft a small crust (miliary abscess) occurred on the surface of the epithelium.

Biopsy 6 (control).—*Sensitivity.*—The area of excision was located in the small of the back. It was relatively insensitive to pressure and mechanical vibration. Stimulation by the alternating current induced a sensation of "burning vibration." This sensation seemed "diffused," and the clear perception of vibration experienced on stimulation of a true vibration spot was lacking. A good pressure-vibration spot was located near, but was not included in, the biopsy specimen. The area was relatively insensitive to temperature stimulation.

Histologic Structure.—Cells resembling the Merkel cells were present, although no nerve ends or fibers to such cells could be found.

There was a rich argentophil reticulum just beneath the epithelium. The section was relatively nonvascular so far as the subepithelial supply was concerned. One Meissner corpuscle was found in this specimen; it was located at the margin of the piece, not near the center. The perivascular arborizations were loose and less noticeable than in the other specimens.

In one of the marginal sections there appeared to be a loop of a vessel showing a thick, cubical muscle cell coat, of the type often associated with the Sucquet-Hoyer canals. It disappeared early and was not found in any of the remaining slides.

In the specimen were several hair follicles, sweat glands, groups of arrector pili muscles and coils of small myelinated nerve trunks.

Biopsy 7.—*Sensitivity.*—The area of excision was located on the ventral side of the arm near the wrist. It was sensitive to pressure and mechanical vibration. Feelings of vibration were elicited by the alternating current. The area was highly sensitive to cold stimulation.

Explanation of Figure 3

Fig. 3.—*A,* section from biopsy specimen 3. Note the Merkel-Ranvier corpuscles in the basal layer and a coarse nerve fiber which is seen to enter the malpighian layer near them. Wilder's silver stain and phosphotungstic acid hematoxylin; magnification, 480.

B, section from biopsy specimen 6. The area was sensitive to pressure, mechanical vibration and vibration by alternating current and highly sensitive to cold stimulation. Merkel-Ranvier cells stood out sharply. At the left side of the papilla there were several capillaries, the presence of which is indicated by several endothelial lining cells. At the right apex of the papilla several nonmedullated nerves appear to enter and end as free fibers in the malpighian layer. Wilder's silver stain and Mallory's phosphotungstic acid hematoxylin; magnification, 400.

Histologic Structure.—The malpighian layer showed the usual number of Merkel cells. Other nerve structures were not well stained. The free nerves in the subepithelial zone either were not stained or were less numerous than in most of the sections studied. No encapsulated corpuscles were found.

This section presented the most highly vascular, subepithelial zone of any biopsy specimen studied. The vessels were unusually numerous and superficial and tended to run parallel to the malpighian layer at right angles, rather than perpendicularly. Many of the capillary walls were surrounded by a very loose network of reticulum and argentophil fibrils resembling nerve endings.

At the tip of the section there was a group of vessels having slightly thicker walls than those just beneath the epithelium, in which cubical muscle cells and numerous nerve endings were found. This was either part of a glomus body or one of the cubical muscle cell extensions connected with a glomus body. At the base of the piece was a bundle of medullated nerves. At the side of the glomus-like body was a myelinated nerve bundle, and one small nerve could be seen to break up into a subepithelial plexus.

Encapsulated nerve end organs and hair follicles were absent. A sweat gland duct and two arrector pili muscles were located near the center of the block.

Biopsy 8.—*Sensitivity.*—The area of excision was located on the dorsal side of the arm near the wrist. It was sensitive to pressure and mechanical vibration. Feelings of vibration were elicited by the alternating electric current. Although vibratory sensitivity could be elicited at several stimulus points within 1 sq. mm. of surface area, the most sensitive point was near the base of a hair. This specimen also contained tissue highly sensitive to heat stimulation.

Histologic Structure.—In the malpighian layer were cells of the Merkel-Ranvier type. No connection between these cells and nerve fibers could be traced with certainty. In the region of the papillae there were sprays of argentophil fibrils continuous with the reticulum and nonmedullated plexuses of the corium. These sprays stained black in the silver preparations and red with the Masson stain. They were far more numerous in the regions of the papillae, where they appeared to enter the malpighian layer and radiate among the epithelial cells. The basement membrane was interrupted at the papillae. In the subcutaneous areas were anastomoses of argentophil fibrils that surrounded the vessels. In some of the first of the serial sections there were several large hair follicles with coils of sweat glands and small nerve trunks with papillary muscles near them. At the lower border of the corium were two vascular canals with coats of smooth muscle cells arranged at right angles to their lumens. In the later sections of the series these two structures joined. A small bundle of medullated nerves lay near the vessel. The vascular structure resembled a loop of a Sucquet-Hoyer canal. Two similar vascular structures occurred in this biopsy specimen. The perivascular plexuses were unusually abundant throughout the specimen.

Biopsy 9 A and B.—This was the only experiment in which any of the original patterns of sensitivity persisted after excision. Therefore the tissue underlying this sensory spot was removed a second time, seven months after the first removal. The first excision extended a depth of less than 2 mm. The second excision included the scar tissue which was formed as a result of the first operation and extended an additional depth of 5 mm. The first excision is described as *A* and the second as *B*.

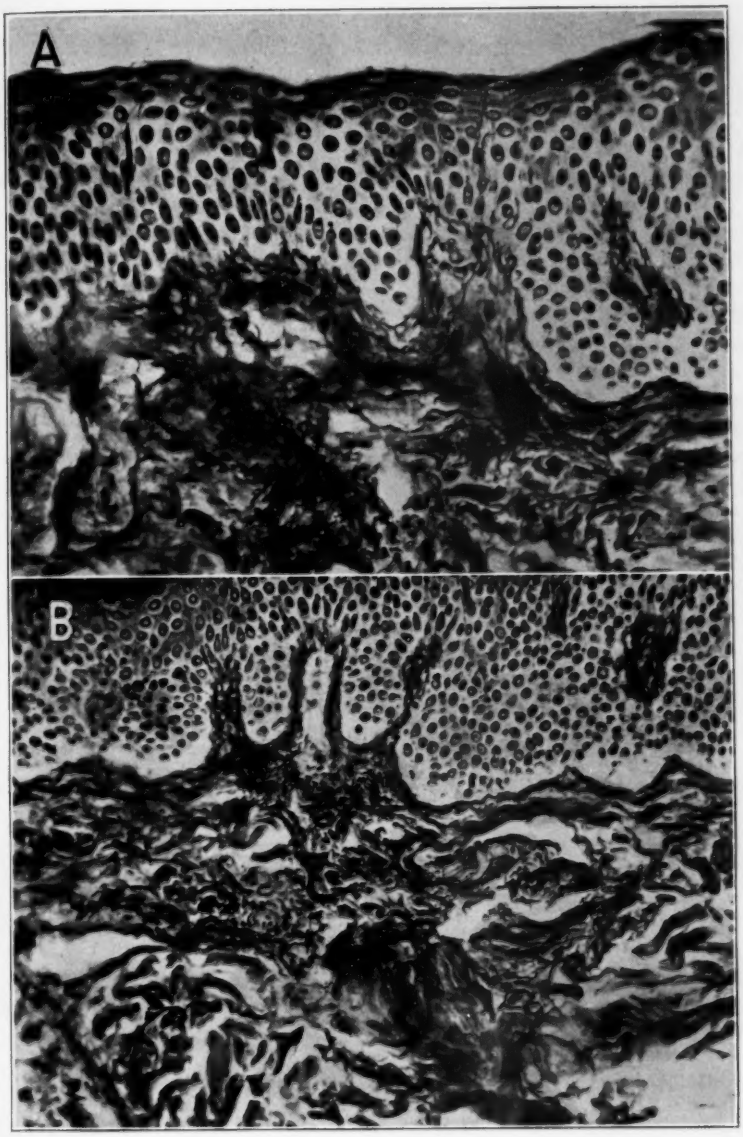

Fig. 4.—Sections from biopsy 5. Note the plexus of nonmedullated nerves in the subepithelial layer, most of which are in close relation to capillaries. In the lower left corner of *B* a bushlike nerve ending in a capillary wall may be seen. In these sections the nerve fibers were black and the collagenous reticulum was brownish. Magnifications: *A*, 400; *B*, 280; Wilder's silver stain and Mallory's phosphotungstic acid hematoxylin.

A. Sensitivity.—The area of excision was located near the middle of the back. The specimen consisted of a piece about 2 by 1 by 1 mm. and a fragment. The area was fairly sensitive to pressure and mechanical vibration. Stimulation by alternating electric current elicited feelings of vibration associated with a pattern of heat. The skin was highly sensitive to heat stimulation.

Histologic Structure.—The block was small and was cut parallel to the surface. Merkel-Ranvier cells were present. A few argentophil (Langerhans) cells stood out clearly with Popoff's stain. They appeared to be fixed epithelial cells in the basal layer. The vessels were of the ordinary arteriole-capillary type with the usual perivascular nerve reticulum. The subepithelial reticulum was not stained. No encapsulated end organs were present. Near the center of the section were three hair follicles. Two were single, while the third had a double papilla, from which two hair shafts could be traced through the malpighian layer. Sweat gland ducts lay on each side of the group of hair follicles. The piece was too superficial to be of much value.

B. Sensitivity.—The specimen was a cone-shaped piece of skin 0.5 cm. in diameter which extended to a depth of 7 mm. and included a part of the subcutaneous adipose layer. One edge of the block had been pulled up to a point, and a small bit of epithelium had been nipped off the apex with the forceps. Two months after the first excision the spot was again highly sensitive to heat. Pressure sensitivity had diminished. Stimulation of the scar tissue by intense mechanical vibration gave the experience of the tissue "vibrating as a mass." No sensitivity could be elicited by the alternating electric current, it being impossible to establish electrical contact through the scar tissue.

Histologic Structure.—The malpighian layer had completely regenerated, although the papillary layer was flattened for a short distance toward one side of the section and the malpighian layer over this area was not cornified. In this area the collagen was abundant and compressed, and with Masson's stain gave a reaction characteristic of scar tissue. There were three sets of hair follicles in the corium, one of which had a double shaft. Each hair follicle was connected with a sebaceous gland. The sweat gland ducts passed entirely through the corium and ended in sets of sweat gland coils in the stratum subcutaneum. Two somewhat tortuous arterioles having circularly arranged muscle coats were situated in the deeper layers of the reticular stratum, and one of them was accompanied by a medullated nerve trunk. No partial or complete glomus bodies were present, and there were no encapsulated sensory organs. The superficial vessels were of the usual arteriolar-capillary-venous type. In short, biopsy revealed no sensory end organs, and nothing was found to explain the sensations of deep pressure and heat. The two vessels with circularly arranged muscle walls could have been related to glomus bodies, but they were not sufficiently typical to be identified as portions of Sucquet-Hoyer canals.

SUMMARY OF HISTOLOGIC OBSERVATIONS IN ALL BIOPSIES

The various structures observed in the biopsy specimens which were thought to be concerned with sensory impulses could be divided into two groups: those that were common to all specimens and those that were found in some and not in others.

Of the first group of structures, several were located in the malpighian layer. These included (*a*) argentophil fibers, which were occa-

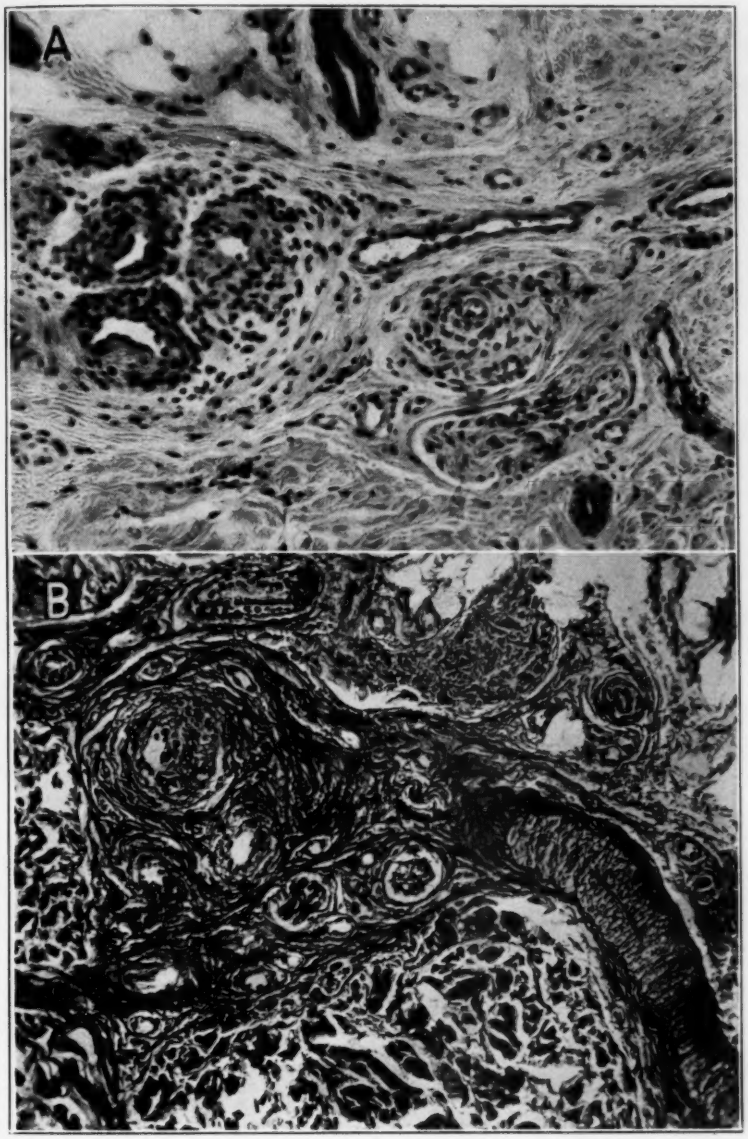

Fig. 5.—*A,* section from the ball of the toe of a traumatically amputated foot, used for comparative studies on arteriovenous anastomoses of the glomus type. Note the coils of proximal arterioles of two glomus bodies. The canal-like structure at the top of the picture is a sweat gland duct. Magnification, 50.

B, section from the same specimen as that shown in *A.* On the left side of the picture is a coil of proximal arterioles, which is seen to be continuous with the Sucquet-Hoyer canal extending downward toward the lower right corner. Two cross sections of a medullary nerve and many nonmedullated nerves can be seen in the periglomic reticular zone. Wilder's silver stain and Mallory's phosphotungstic acid hematoxylin; magnification, 50.

sionally seen to penetrate the malpighian layer and which probably were the free, nonmedullated nerve filaments regularly described and illustrated in textbooks of histology; (*b*) cells with solidly staining, round or crescent nuclei, surrounded by vacuoles which were classified as Merkel-Ranvier corpuscles, whether the respective connective nerve fibers could be found or not, and (*c*) pigmented argentophil cells of the Langerhans type. Epithelial cells in mitosis and resolution which had to be differentiated from Merkel-Ranvier corpuscles and from Langerhans cells were regularly present in the basal layers.

Other nerve structures common to all of the biopsy specimens were observed in the connective tissue beneath the epithelial layer. Here were filaments which took the silver stains but did not react to phosphotungstic acid hematoxylin as collagen does. Some of these were thin fibers with typical sheath nuclei along their courses; these undoubtedly were medullated nerves. Other fibers which appeared to be identical, save that the nuclei were absent, remained in question because none of the technical methods used by us could be depended on to differentiate them with certainty from the fine collagenous reticulum. Sheath-accompanied, nonmedullated nerves followed the courses of all the blood vessels, whether arterioles, capillaries or veins. They intermingled with the perivascular reticula and accompanied them to the tips of the papillae. In places the subepithelial and perivascular fibrils could be seen to enter the lower part of the malpighian layer and to spread out for a short distance among the epithelial cells. Such radiating fibers stained black with Wilder's method and red with Masson's trichrome stain and did not stain at all with Bodian's silver method or with Mallory's phosphotungstic acid hematoxylin. Some were nerve fibers, and others may have been either reticular fibers or elongated epithelial fibrils.

The greatest individual variation noted in the biopsies, so far as regularly observed fibers were concerned, was the relative number of the small vessels and their accompanying perivascular nerves. This appeared to indicate that some of the pieces had a much more abundant sensory supply than others.

Of the second group of structures, that is, those found in some biopsy specimens and not in others, that most commonly seen was a small vessel without an elastic coat which had cubical or low columnar muscle cells circularly arranged. These cells corresponded to the coat of the Sucquet-Hoyer canal called "neuromuscular" by Masson. Of the punch sections taken for the study of the glomus body from autopsy materials and amputated extremities, similar canals with muscular coats were constantly observed to be connected with glomus bodies. Two of our experimental biopsy specimens contained actual loops of glomus canals of the more superficial kind. These channels were accompanied

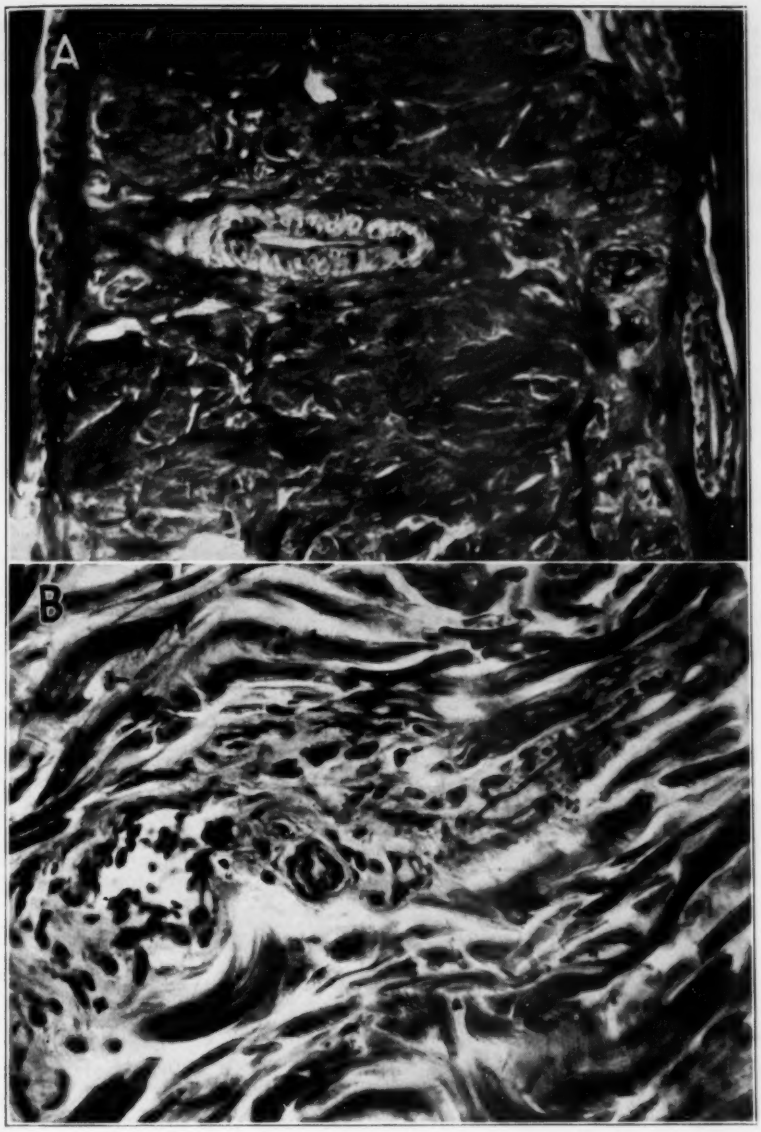

Fig. 6.—*A*, section from the same specimen, showing a small superficial Sucquet-Hoyer canal. This type of canal occurred one or more times in three of the experimental biopsy specimens and was considered evidence of the presence of glomus bodies in the areas bordering on the specimen. The structures at opposite sides of the picture are sweat gland ducts. Masson's stain; magnification, 130.

B, section from the ball of an amputated toe used for comparative studies. Note a small vein at the left below the center, a small arteriole near the center and the cross section of a muscular-walled canal at the right, which is similar to the canal shown in *A*. Several nonmedullated nerves with sheath nuclei may be seen just above the canal. Fixed in Cajal's fluid and stained with Bodian's stain and phosphotungstic acid hematoxylin; magnification, 240.

by small nerve trunks, and in several of the Wilder and Bodian stains (counterstained with phosphotungstic acid hematoxylin) nerve fibers could be seen to spread out in numerous small ramifications and to enter the muscular coat.

In the 9 biopsy specimens studied, only one Meissner corpuscle was found, notwithstanding the fact that almost every third section was stained with Masson's trichrome stain. The last biopsy specimen extended down into the areolar layer, and it, in common with the others, failed to show Pacini corpuscles or Krause end bulbs. In many sections structures suggesting Ruffini end organs were seen, but on being traced serially, from section to section, they proved to be parts of perivascular networks, not encapsulated units of any kind. In an occasional section sheath nuclei were penetrated by nonmedullated fibers. These could be found almost anywhere in the corium.

In all of the 7 biopsy specimens taken because of their known response to vibration and pressure stimuli, Markel-Ranvier cells, free endings in the epithelium, subepithelial networks and perivascular neuroreticular baskets were present and varied only in their relative numbers. None contained Meissner corpuscles or any of the deeper, encapsulated sensory corpuscles. Two contained loops of Sucquet-Hoyer canals and 3 others a type of canal, with cubical muscle cell walls, which is often seen in connection with glomus bodies elsewhere.

In 2 control specimens the same general set of structures was found, but less frequently. One contained a Meissner corpuscle at the margin. One contained a canal with a cubical muscle cell coat, and the other did not. As may have been gathered, there was practically no difference histologically between the vibration-pressure areas and the so-called controls. Actually there is no such thing as an area of skin devoid of all sensory reaction to stimuli. Some points are relatively sensitive and others relatively nonresponsive. The difference in reaction appears to be due to the convergence of sensitivity at a given point with radiating zones of less sensitivity about it.

Since no sensory end organs were found to which the senses of vibration and pressure could be allotted, other structures came up for discussion as possible indirect interpreters of the sensations. The miliary abscesses undoubtedly gave a false impression in the specimens in which they occurred. Particularly was this true in biopsy specimen 4, in which the sensation was described as "stinging pain." Hair follicles, sebaceous glands, sweat glands and arrector pili muscles did not appear promising as indirect sense organs. Five of the 8 biopsy specimens and 1 of the 2 control specimens contained portions of arteriovenous anastomoses of the glomus type. Relatively little is known of this structure in man, and while it is not considered primarily a nerve structure, there is indirect evidence of its auxiliary action.

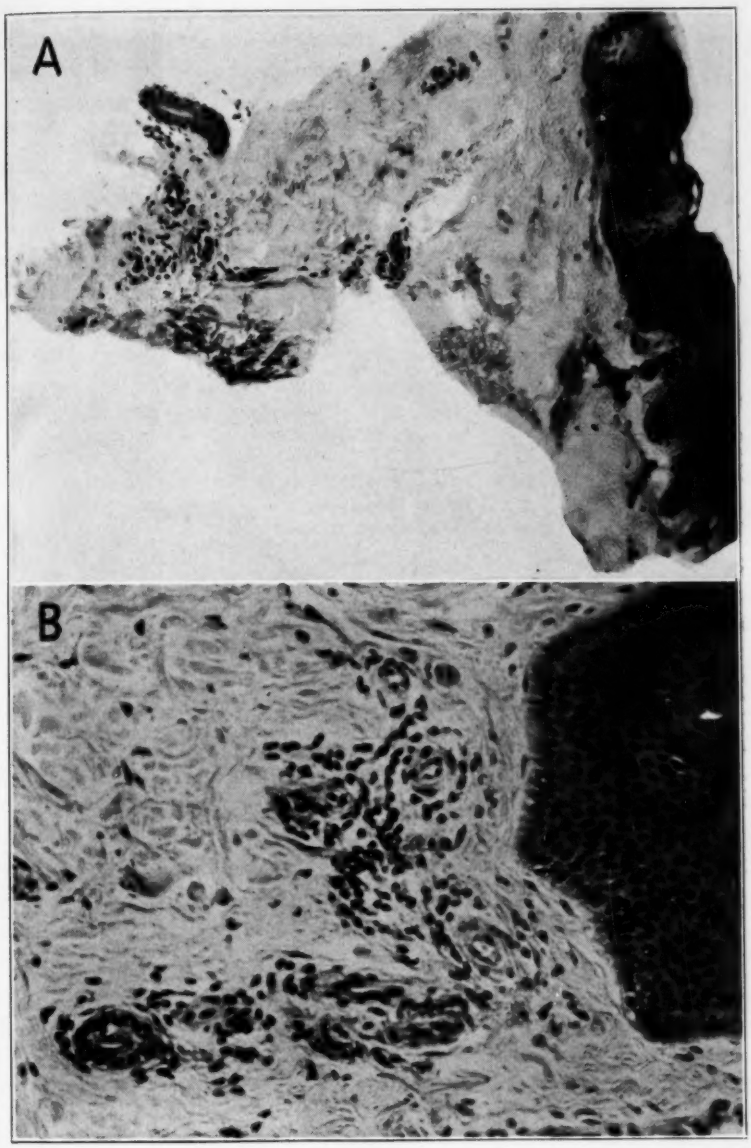

Fig. 7.—*A*, section through entire biopsy specimen 5. At the lowest point of the specimen an almost complete glomus body may be seen, with a sweat gland duct above it. Magnification, 25.

B, section from the ball of a toe included for comparison. Note the very small coils of an arteriovenous anastomosis just beneath the malpighian layer. This photograph was taken to show that these structures are sometimes very superficial. A cross section of a sweat gland duct is seen in the lower left corner. Magnification, 240.

The glomus is a type of arteriovenous anastomosis having a very rich nerve supply. That portion known as the Sucquet-Hoyer canal has such an intimate nerve mechanism that its muscular coat was called a "neuromuscular" coat by Masson. The tumors which arise from the glomus are generally described as "exquisitely painful." Grant [29] and Clark and Clark,[30] by means of transparent chambers placed in the ears of rabbits, have demonstrated the nerve supply by injections of methylene blue (methylthionine chloride) and have observed continuous contractions of the arteriovenous anastomosis over periods of days after stimulation by cold or nerve injury. The sensations of vibration and pressure, as well as the heat control of the skin, are known to decrease with age. Popoff described atrophy and sclerosis of the glomus body in the aged, and these changes were obvious in some of the punch specimens obtained post mortem from the fingers and toes of human subjects.

Mainly for these reasons we directed our attention to the glomus.

STUDIES OF THE GLOMUS AND RELATED NERVE SUPPLIES

Our experimental biopsy specimens contained parts of glomus bodies but no entire glomus structure; so in order to acquire a more direct knowledge of the glomus body and to examine its nerve supply for ourselves, we studied punch specimens from the tips of the fingers, from the balls of the toes of amputated legs and from surgical specimens, such as the skin over the breast, nipple and areolar areas, skin at the side of moles removed from the face, lips and other parts of the body, and a number of foreskins removed by circumcision. With Masson's [31] and Popoff's [26] articles as guides, something over 500 slides of serial sections were studied, the majority of them containing glomus bodies. A complete review of the literature on natural arteriovenous anastomoses and glomus bodies has been made in both of the aforementioned articles and by Clark [32] and will not be repeated here.

Masson described the glomus structure as occurring with diminishing frequency in the bed of the nail, the palmar digital pulp and the terminal

29. Grant, R. T.: Observations on Direct Communications Between Arteries and Veins in the Rabbit's Ear, Heart **15**:281, 1930.

30. Clark, E. R., and Clark, E. L.: Observations on Living Preformed Blood Vessels as Seen in a Transparent Chamber Inserted into the Rabbit's ear, Am. J. Anat. **49**:441, 1932; Observations on Living Arterio-Venous Anastomoses as Seen in Transparent Chambers Introduced into the Rabbit's Ear, ibid. **54**:229, 1934; The New Formation of Arterio-Venous Anastomoses in the Rabbit's Ear, ibid. **55**: 407-467, 1934.

31. Masson, P.: Le glomus neuromyo-artériel des régions tactiles et ses tumeurs, Lyon chir. **21**:257-280, 1924.

32. Clark, E. R.: Arterio-Venous Anastomoses, Physiol. Rev. **18**:229-247, 1938.

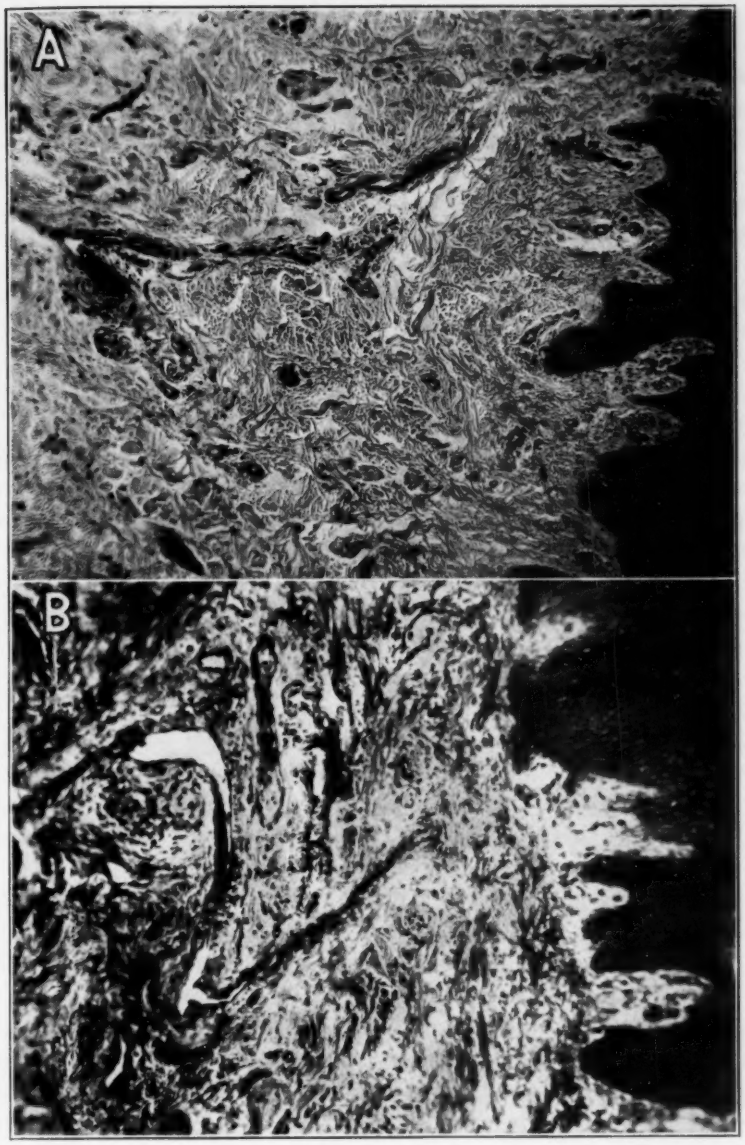

Fig. 8.—*A*, section from the ball of the toe for comparison. Note the arteriovenous anastomosis of the glomus type in the lower part of the photograph, with a portion of a Sucquet-Hoyer canal extending upward toward the epithelial layer, and the presence of a comparatively large medullary nerve within the periglomic reticulum. Magnification, 130.

B, section from the same specimen as that shown in *A*. Note the two proximal arterioles and a portion of the Sucquet-Hoyer canal with a branch extending upward almost through the reticular zone. Whether this prolongation belonged on the venous or on the arterial side was not clear. It had a profuse nerve supply and a muscular wall, the cells of which appeared cubical in cross section, and it was a component part of the glomus body. Masson's stain; magnification, 240.

and middle phalanges and gave it the name *glomus neurovasculaire*. It is a thick-walled, arterial segment which may follow a straight or winding course and empty into a wide, thin-walled vein, the whole structure making a sort of ball, or glomus. The arterial segment has no elastic layer and has a thick muscle wall of several layers, of which the inner ones are typical smooth muscle and the outer an epithelioid type of modified, smooth muscle cells. Outside of this is a "rich muff" of nerves, which consists both of nonmedullated fibers extending out from the network about arteries and veins and of irregular, nodulated, nonmedullated fibers continuous with the dermal plexus. Masson stated that the nerves could be followed on occasion to endings among the epithelial cells. He found these structures in fetuses in the fourth and fifth month and observed that they were normally present in adults. In addition, he described 47 glomus tumors.

Clark and Clark showed that during dilatation Sucquet-Hoyer canals measured from 20 to 40 microns at their narrowest diameter. However, typical anastomoses having a diameter no greater than 5 microns were not infrequent. They stated that two hundred and fifty-six times as much blood could pass through an anastomosis 40 microns in diameter as through a capillary 10 microns in diameter. Popoff measured individual Sucquet-Hoyer canals and found variations from 120 to 220 microns in the pad of the toe and from 60 to 150 microns in the nail bed.

Popoff studied 840 blocks of tissue containing glomus bodies. He found such structures distributed almost exclusively over the ventral surfaces of the hands and feet. Clark [32] observed them in rabbit ears, and others have described them in the skin of the elbow, knee, lip, cheek, nose, temple, eyelid, forehead and ear.

From our sections we concluded that they are present to a greater or lesser extent in the skin of all portions of the body, but are probably far more numerous in the ventral surfaces of the hands and feet and in the lips. We found numerous thin-walled and normally dilated arteriovenous anastomoses in the foreskins of infants.

Popoff preferred the term "arteriovenous anastomosis of the Sucquet-Hoyer type" to the term "glomus." He enlarged on the studies of Masson and defined the term used by him as follows: The Sucquet-Hoyer canal includes the portion of the channel connecting the artery and the vein, that is, the arteriovenous anastomosis. The entire unit includes (1) the afferent artery; (2) the Sucquet-Hoyer canal, which may have one, two or three separate units connnected with a single afferent artery; (3) preglomic arterioles nourishing the glomus; (4) a periglomic zone furnished with a neuroreticular mechanism, which controls the function of the Sucquet-Hoyer canal; (5) a special system of collecting veins, and (6) the outer lamellated collagenous tissue.

Clark and Clark's interpretation of the structure of arteriovenous anastomoses was reached after studying the circulation in the rabbit's ear through artificially introduced windows over a period of several months. Most of the arteriovenous anastomoses were somewhat tortuous, rather than coiled in the manner described by Masson and Popoff. There was a tendency for several arteriovenous anastomoses to occur in close proximity to each other. Had they been observed in contracted, fixed tissues, such a group of vessels could have produced an appearance closely comparable to the coiled forms seen in human biopsy specimens. In fact, we think it likely that many of the arteriovenous anastomoses seen in our preparations were multiple, short, tortuous canals rather than single or double channels twisted into a few compact coils, according to the interpretation of Masson. The three main anatomic divisions described in the glomic arteriovenous anastomoses were easily differentiated by Clark and Clark. These consisted of the afferent arterial portion, the thicker-walled muscular portion (comparable to the Sucquet-Hoyer canal) and the thin-walled venous portion. They observed the formation of new arteriovenous anastomoses, both temporary and permanent, and the disappearance of some of the old anastomoses.

From our study of the glomus, we have observed several things that may be anatomically important to the reflex sensory control of the circulation of the skin. As has been pointed out, there were the arteriovenous anastomoses of the true glomic type, of the general makeup described by Sucquet-Hoyer, Masson, Popoff and many others, and these were generally grouped about coils of sweat glands in the subcutaneous stratum of the skin. We have observed a structure in connection with these bodies that appears not to have attracted much attention. It consists of a small canal located on the venous side of the arteriovenous anastomosis; yet it has a well developed smooth muscle wall. In a few such structures were found both an internal longitudinal layer of cells and an outer layer consisting of a single, or at most a double, row of circular muscle cells which appear cubical on cross section. Usually only the circular rows were present. These muscular channels did not join the returning veins but continued upward toward the malpighian layer and papillary stratum and either disappeared or became continuous with capillaries. In a few of the better preparations they were seen to have an abundant nerve supply. They formed a part of the glomus, but were not definitely either arterioles or veins. In any case, they shared in the rich nerve supply of the glomus body. In addition to the well differentiated glomus bodies, there were numerous coils of arterioles, some with and some without elastic lining. Many of these also appeared to be small arteriovenous anastomoses. They occupied the reticular stratum chiefly. It should also be added that an occasional arteriovenous anastomosis of the small glomus type could be

found both in the reticular and in the papillary stratum. Many authors have mentioned variations in the size of glomus bodies and have brought out the fact that some are straight, some tortuous and some coiled in tight, ball-like knots. Our observations agree with these statements. In several sections taken from the neighborhood of new growths about the lips, we found that the Sucquet-Hoyer canals were generally straight. They were also straight, or slightly tortuous, in the specimens of foreskins removed by circumcision on the sixth day of life. The compactness and size of the typical tortuous glomus bodies appeared to vary with the location in the body and with the age of the subject. Those in the digits showed considerable variation in size when compared with each other in the same location and as a rule were more compactly coiled than those from looser portions of skin. The glomus units appeared less tightly woven in children and in the aged than they did during active, adult life. In later years they appeared relaxed and often more or less hyalinized.

CONCLUSIONS

1. The excision studies failed to substantiate the conventional claim that the cutaneous pressure qualities are mediated by specific sense receptors, since the sites for study were selected with extreme care and no such receptors were found.

2. The possibility that the neurovascular system of the skin operates either in a direct or in an indirect manner in the mediation of cutaneous pressure and vibration is suggested by two observations.

(*a*) The neurovascular system of the skin contains certain structural units richly endowed with a nerve supply, surrounded by regions of less nerve concentration.

(*b*) Biopsy specimens taken from the cutaneous areas highly sensitive to pressure and vibratory stimulation were found to contain a richer afferent arterial nerve supply than the specimens taken as controls in which the tissue was less sensitive to pressure and vibration.

3. The presence in several of the biopsy specimens from spots sensitive to pressure and vibration of certain tubular, straight canals having muscular walls which appeared to unite the glomus bodies of the stratum subcutaneum with the capillary zone of the stratum papillare and the presence of its rich reticular nerve supply served to strengthen our postulation that the arteriovenous anastomoses in the skin are in some way related to sensory interpretations.

EFFECT OF NICOTINIC ACID AND RELATED SUBSTANCES ON THE INTRACRANIAL BLOOD FLOW OF MAN

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MILTON ROSENBAUM, M.D.

AND

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CINCINNATI

The dilating action of nicotinic acid on the blood vessels of the skin and probably of the skeletal muscle has been well established. Bean and Spies [1] observed that nicotinic acid and certain other closely related compounds caused widespread flushing and elevation in temperature of the skin. Abramson, Katzenstein and Senior,[2] using the venous occlusion plethysmograph, showed that nicotinic acid significantly increased the blood flow to both the distal and the proximal portions of the extremities. They concluded that the augmentation of blood flow in the proximal portions occurred in both skin and skeletal muscle. That the nicotinic acid caused active dilatation of the blood vessels was evidenced by the fact that no significant changes in blood pressure occurred. Moore [3] observed that nicotinic acid dilated the pial vessels of the cat and that it caused an elevation of cerebrospinal fluid pressure in 2 human subjects. From somewhat limited observations he concluded that nicotinic acid increased cerebral blood flow in man and recommended its use in the treatment of multiple sclerosis.

Since the latter studies concerning the effect of nicotinic acid on cerebral blood flow are not conclusive, we have investigated its action

* Aided by a grant from the Rockefeller Foundation.

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1. Bean, W. B., and Spies, T. D.: A Study of the Effects of Nicotinic Acid and Related Pyridine and Pyrazine Compounds on the Temperature of the Skin of Human Beings, Am. Heart J. **20**:62-76, 1940.

2. Abramson, D. I.; Katzenstein, K. H., and Senior, F. A.: Effect of Nicotinic Acid on Peripheral Blood Flow in Man, Am. J. M. Sc. **200**:96-102, 1940.

3. Moore, M. T.: Treatment of Multiple Sclerosis with Nicotinic Acid and Vitamin B_1, Arch. Int. Med. **65**:1-18 (Jan.) 1940.

on cerebral blood flow by a more direct method, recently developed in this laboratory. In addition, we have compared its action (on cerebral blood flow) with that of nicotinic acid amide, a drug which has pellagra-curative properties but which, unlike nicotinic acid, does not dilate the blood vessels of the skin. Finally, we have investigated the effect on cerebral blood flow of quinine nicotinate, a related drug that causes flushing of the skin and presumably dilates the blood vessels of the skin.

METHOD

The method for estimating the volume flow of blood through the intracranial contents of man has been described in detail elsewhere.[4] Briefly, it consists in the measurement of the rate of cerebrospinal fluid displacement through a large lumbar puncture needle during sudden compression of the veins of the neck for a few seconds. The principle is similar to that utilized in the plethysmographic measurement of blood flow in the extremities. Compression of the neck veins is effected by sudden inflation of an especially designed rubber cuff which surrounds the neck. By using a constant occlusive pressure (60 mm. of mercury) in the cuff and a constant cerebrospinal fluid pressure (200 mm. of water), all cerebrospinal fluid displacement rates obtained throughout a given experiment bear the same relation to the total intracranial blood flow.

Successful studies, using nicotinic acid or related substances, were completed in 16 instances. In each, a series of cerebrospinal fluid displacement rates was obtained over varying periods ranging up to twenty minutes. The patient was then given intravenously 20 to 50 mg. of nicotinic acid (or 50 to 75 mg. of nicotinic acid amide or 42 mg. of quinine nicotinate). Another series of displacement rates was then obtained over varying periods ranging up to sixty-two minutes. Determinations were never made at intervals of less than one minute.

All determinations were made during periods when the patient was as quiet and relaxed as possible. A running record of the pulse rate, respiratory rate and blood pressure was kept throughout each study. Subjective and objective symptoms and signs were recorded. In each case the dose of nicotinic acid or quinine nicotinate used was sufficient to cause flushing and a sensation of warmth in the skin.

RESULTS

The results of these studies are recorded in the table. In all of the studies in which nicotinic acid was administered (20 to 50 mg. intravenously) it caused a significant increase in the total intracranial blood flow. The increase followed quickly on the intravenous injection of the drug, and when the study was prolonged the increased pressure was maintained and gradually returned to normal. The intracranial blood flow was still significantly elevated forty-five minutes after the injection of 50 mg. of nicotinic acid. The augmentation in intracranial flow began shortly after the flushing of the skin and the feeling of warmth. The feeling of warmth was the first to disappear. The flush was apparently

4. Ferris, E. B., Jr.: Objective Measurement of Relative Intracranial Blood Flow in Man, with Observations Concerning the Hydrodynamics of the Craniovertebral System, Arch. Neurol. & Psychiat. **46**:377 (Sept.) 1941.

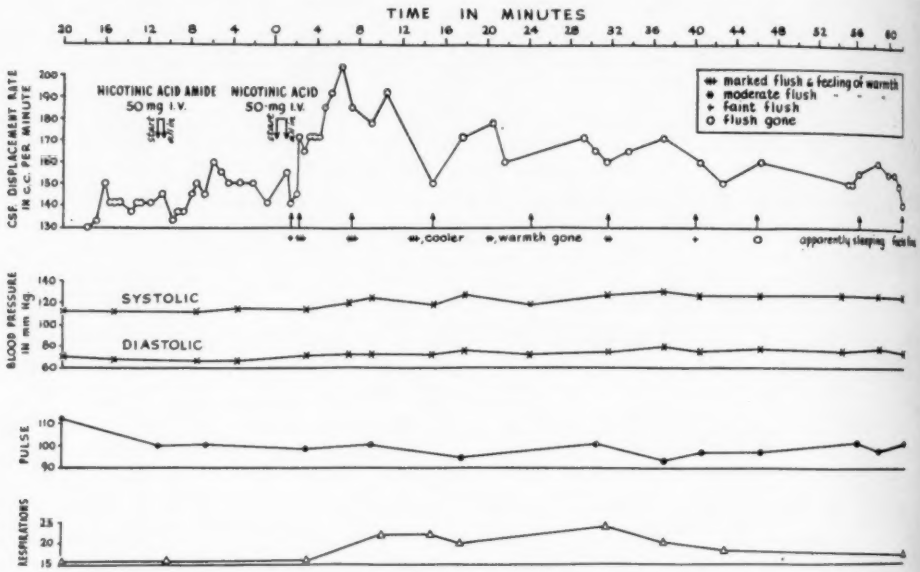
Cerebrospinal Fluid Displacement Rates, Measured in Cubic Centimeters per Minute, Determined Before and After the Intravenous Injection of Nicotinic Acid, Quinine Nicotinate and Nicotinic Acid Amide *

Experiment Number	Cerebrospinal Fluid: Rate of Displacement Before Injection of Drug	Average	Intravenous Dose of Drug, Mg.	Cerebrospinal Fluid: Rate of Displacement After Injection of Drug	Average
			Nicotinic Acid		
57	118, 126, 114, 126	121	20	155, 165, 171, 160	163
58	133, 126, 133, 141, 133, 141	134	20	171, 160, 160, 150, 145	157
60	141, 126, 150, 133, 133, 133	136	20	150, 171, 160, 150, 160, 150, 160, 171, 150	158
68	86, 89, 77, 86, 80, 86 83, 83, 92, 92, 96, 80, 77	85	40	100, 109, 109, 104, 92, 109	104
71	96, 90, 92, 89, 100, 100, 96, 92, 104, 120, 109, 104	99	20	126, 109, 109, 104, 109, 120	113
93	83, 86, 80, 80, 81, 72, 75, 81, 80	80	40	92, 97, 96, 88, 95	94
127	160, 150, 150, 160, 172, 172, 160, 141, 160, 150, 160, 155, 150, 155, 150, 155	155	50	172, 172, 178, 178, 172, 178, 172, 178, 166, 172, 178, 185, 166, 185, 166, 178, 178, 185, 185	176
129	123, 114, 117, 109, 112, 120, 133, 130	120	40	150, 155, 137, 150, 145, 137, 137, 141, 130, 141	142
133	130, 133, 150, 141, 141, 141, 137, 141, 141, 141, 145, 133, 137, 137, 145, 150, 145, 160, 155, 150, 150, 150, 141	143	50	155, 141, 145, 171, 165, 171 171, 171, 185, 192, 204, 185, 178, 192, 150, 171, 178, 160, 171, 165, 160, 165, 171, 160, 152, 150, 160, 150, 150, 155, 160, 155, 155, 150, 141	170
	Total average.....	119		.....	142
			Quinine Nicotinate		
131	112, 120, 114, 92, 111, 123, 111	112	42	120, 126, 145, 111, 120, 141 133, 141, 137, 145, 114, 120, 130, 114, 117, 133, 104, 114, 117, 104, 133, 137, 104, 137, 109	124
132	109, 109, 133, 133, 109, 107, 120, 130, 126, 111, 109, 111, 120	117	42	126, 133, 107, 111, 126, 130, 130, 114	122
134	141, 141, 141, 137, 141, 141, 137, 137, 137, 145, 145	140	42	147, 141, 141, 150, 155, 145, 171, 160, 165, 165, 165, 141, 160, 150, 145, 145, 155, 150, 150, 150, 155, 165, 150, 160, 150, 160, 137, 150, 150, 160, 155, 160, 160, 155, 150, 155, 160, 130, 155, 160, 165, 155, 155, 160	154
	Total average.....	123		.....	133
			Nicotinic Acid Amide		
124	141, 150, 145, 160	149	50	141, 155, 141, 160, 150, 150, 155, 141, 130, 160, 133, 150, 141, 141, 141	146
127	160, 150, 150, 160, 185, 172, 160, 141	159	50	160, 150, 150, 160, 155, 150, 155, 150, 155	154
129	130, 114, 117, 141	125	75	109, 112, 120, 138, 130	122
133	130, 133, 150, 141, 141, 141, 137, 141, 141, 141	139	50	145, 133, 137, 137, 145, 150, 145, 160, 155, 150, 150, 150, 141	146
	Total average.....	143		.....	142

* The determinations of the displacement rate were made at intervals of sixty to ninety seconds, on the average. The determinations are listed in consecutive order.

gone while the flow was still elevated. The increase in cerebral blood flow was not accompanied by a significant change in arterial pressure (figure). In 9 cases the average control flow was 119 cc. per minute and the average maximum flow following the intravenous administration of nicotinic acid was 142 cc. per minute (table).

Quinine nicotinate was used in the study of 3 persons. The effects of the intravenous administration of 42 mg. of quinine nicotinate were comparable to those obtained with nicotinic acid, although they were not as marked. It is to be expected that quinine nicotinate in comparable doses will not have the same effect on the cerebral blood flow as nicotinic acid, since quinine makes up a considerable portion of the molecule of



Effect of nicotinic acid amide and nicotinic acid on the cerebrospinal fluid displacement rate, blood pressure, pulse rate and respiratory rate. The case is that of a white woman aged 40, with a paranoid reaction and cortical atrophy (as shown in an encephalogram).

this preparation. The average control flow for these 3 persons was 123 cc. per minute, and the average maximum flow after administration of quinine nicotinate was 133 cc. per minute (table).

Nicotinic acid amide was administered intravenously to 4 patients in doses of 50 to 75 mg. This drug did not significantly alter the intracranial blood flow (table), nor did it cause flushing of the skin. In 3 persons (cases 127, 129 and 133) in whom nicotinic acid amide failed to alter the intracranial blood flow subsequent administration of nicotinic acid caused a definite increase (figure).

The average cerebral blood flow for the 4 persons to whom nicotinic acid amide was administered was 143 cc. per minute before and 142 cc. per minute after injection of the drug.

COMMENT

The increase in intracranial blood flow which follows the administration of nicotinic acid and quinine nicotinate occurs in the absence of significant change in the blood pressure. Therefore it appears that these drugs have an active dilator effect on certain intracranial vessels. Since the method used in this study determines total intracranial flow, it does not indicate which of the intracranial blood vessels are affected. The fact that Moore [3] noted an increase in the width of the pial vessels of the cat after the injection of nicotinic acid suggests that these vessels, at least, are involved in the reaction.

It is apparent that the dilator effect of these substances on the intracranial vessels roughly parallels the reaction of the skin. Derivatives of nicotinic acid which do not cause flushing of the skin probably will not increase the rate of intracranial blood flow. This is true of nicotinic acid amide (table). Since nicotinic acid amide is as effective as nicotinic acid in alleviating certain of the symptoms of pellagra, it is probable that the relief of nervous manifestations of nicotinic acid deficiency does not depend on the dilator effect of this drug on the intracranial blood vessels.

SUMMARY

Nicotinic acid and quinine nicotinate administered intravenously increase the intracranial blood flow for periods lasting from twenty to sixty minutes. This effect, which parallels the flushing of the skin, diminishes gradually after the height of the reaction, which occurs within several minutes of the injection.

Nicotinic acid amide has no significant effect on the total intracranial blood flow; neither does it cause flushing of the skin.

Mr. Nathaniel Brower, Ph.D., and Mrs. Jane K. Friedlander gave technical assistance.

MUSCULAR SHORTENING AND DYSTROPHY

A HEREDOFAMILIAL DISEASE

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We had the opportunity to observe a family of French-Canadian descent in which all the members for three generations showed a symptom complex to our knowledge not heretofore described in the literature. At first this disease seemed to be related to the Klippel-

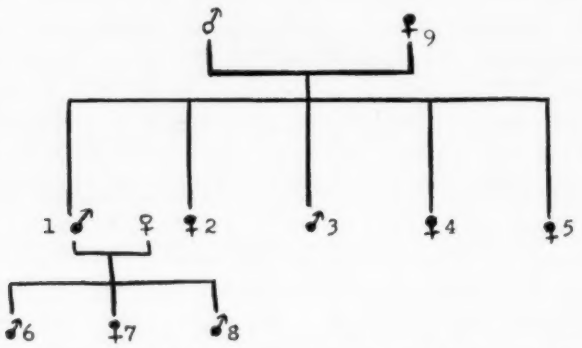

Fig. 1.—Family tree. Numbers correspond to those in the case histories.

Feil syndrome, on the one hand, and to progressive muscular dystrophy, on the other. However, a more precise investigation revealed a familial disease of quite another character.

The members of the second generation showed the most characteristic picture of the disease and will be described first. Data on the first generation were obtained from descriptions given by other members of the family (fig. 1).

CASE 1.—A. P., a 37 year old man, was unable to bend his head forward normally, either actively or passively. The muscles at the back of the neck seemed too short and too tense to permit normal flexion. However, the flexor muscles themselves

From the Joseph H. Pratt Diagnostic Hospital.

This study was made with the aid of the Rockefeller Foundation, the Godfrey Hyams Trust Fund and the Charlton Fund.

were normal in function. Movement of the sternocleidomastoid muscles and vertical rotation of the head were also normal. The patient gave the impression of having a neck too short and, at the same time, too broad. The external borders of the neck, formed by the lateral parts of the trapezius muscles, were out of place and seemed to be broader than usual (fig. 2). The cranial nerves and the muscles of the face were normal.

The long muscles of the back showed the same shortness as the muscles of the neck. When the patient leaned forward, the tendons of these muscles were abnormally tense and a full bending movement was prevented. The flexion was performed not with the vertebral column but with the hip and knee joints.

The muscles of the shoulder were normal. The flexor muscles of the upper portion of both arms were abnormally underdeveloped, and their power was accordingly diminished. Complete extension of the arms at the elbow joints

Fig. 2.—"Webbed neck," produced by tension of the shortened trapezius muscles.

was impossible because the flexors were too short and became tense when the arms were stretched (figs. 3 and 4). All the other muscles of the arms were normal. There were no fibrillary twitchings. Electrical examination did not reveal any anomalies. There were no sensory disturbances. The deep reflexes of the arms were absent. No signs of involvement of the pyramidal tract were found.

Full extension of the legs at the knee joints were not possible because the flexors of the lower portions of the legs were too short and showed premature tension when the legs were stretched. However, this tension was not quite so pronounced as in the flexors of the arms. The dorsiflexion of the feet was imperfect because the muscles of the calf became prematurely tense. Except for slightly diminished muscular power of the shortened flexors of the lower portion of both legs, there were no other pathologic changes in the leg muscles. (For discussion of the gluteal muscles, see the next paragraph.) There were no fibrillary twitchings in the legs. The response to electrical stimulation was normal.

The patellar reflexes were present but diminished. The left achilles reflex was present and the right absent. There were no pyramidal signs or sensory disturbances.

The patient was unable to sit up from a recumbent position while holding his arms crossed over his chest. He was able to do so only when his thighs were pressed against the table on which he was lying. This inability therefore could not

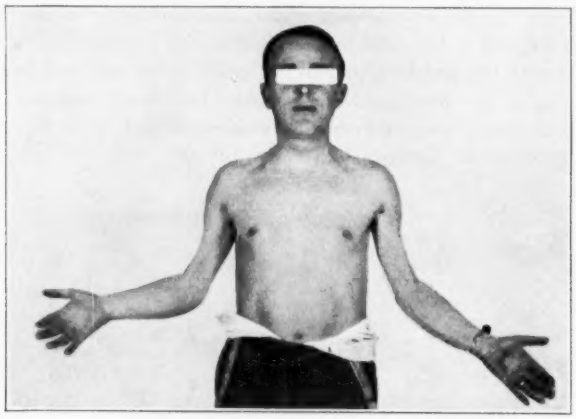

Fig. 3.—Limitation in stretching the arms because of the shortening of the underdeveloped flexor muscles.

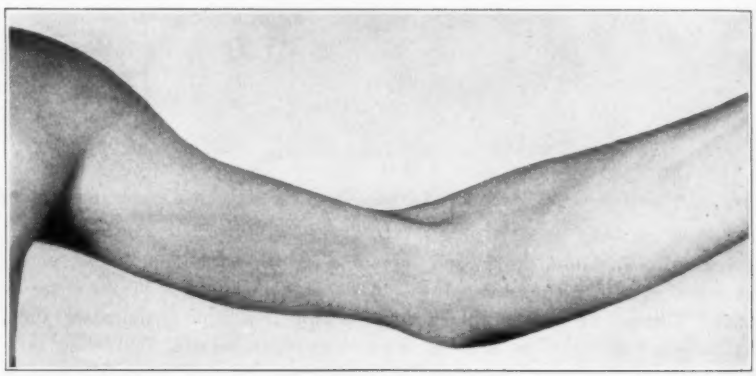

Fig. 4.—The sharp contours of the strained flexors are pronounced.

be caused by weakness of the iliopsoas muscles, the normal power of which, moreover, was shown by direct examination. The difficulty in sitting up was probably the result of weakness in the gluteal muscles, since the thighs could not be pressed against the table. The fact that the patient could not step up onto a chair except with a certain swing may also be considered evidence of the impairment of these muscles. Yet this weakness could not have been marked, for when the patient was standing he could arise from a stooped position without any difficulty.

The muscles of the abdominal walls were normal. The abdominal reflexes were present.

The patient was in good health, was psychically normal and had no difficulties in his occupation as an attendant in a filling station. Although he had noticed these anomalies in his childhood, he had never sought medical advice concerning them and came to the hospital only at our request, because the same malformations had already been discovered in his sister (case 2).

CASE 2.—O. P., a 35 year old woman, a sister of the patient in case 1, came to the hospital with complaints of pain in both lower quadrants of the abdomen, especially at the time of menstruation. Her menstrual periods, which had begun at the age of 13, were accompanied by severe dysmenorrhea. She also complained more recently of daily headaches and a heavy feeling of pressure in the neck and at the back of the head.

Fig. 5.—"Webbed neck"; limitation in stretching the arms; underdevelopment of the muscles of the upper portions of the arms.

While examining the patient one of us discovered that her neck was of peculiar shape and that there were abnormalities of her muscles. These muscular anomalies, which had nothing in common with the complaints for which she was admitted, proved to be important on detailed examination. The patient said that she had first noticed these anomalies at the age of 8 and that although she had not paid much attention to them, she was sure they had increased slightly.

The results of examination were as follows: The cranial nerves were normal. The patient showed the same limitation of motion in bending the head and in stooping as did her brother (case 1). The shortness of the neck and the marked lateral widening (so-called webbed neck) were even more pronounced in her case (fig. 5). She was also unable to stretch her arms at the elbow joints. Not only were the flexor muscles of the upper portions of the arms small, but the extensors were also poorly developed. The power of the flexors was diminished. The deep reflexes were absent. There were no fibrillary twitchings. The electrical response was normal. No sensory changes were found.

The patient also found it difficult to sit up from a recumbent position. The gluteal muscles, too, showed some weakness, which was evident from the fact

that she found it impossible to step up onto a chair without holding on to its arms. In addition, she had a waddling gait, like that seen in cases of muscular dystrophy. The muscular power of the legs was otherwise normal. The patellar reflexes were very weak; the ankle reflexes were present. There were no fibrillary twitchings, and response to electrical stimulation was normal. No sensory changes were found.

Roentgenographic examination did not show any anomalies of the skull, extremities or vertebrae. There was no anomaly of the cervical portion of the spine, such as occurs in the Klippel-Feil syndrome. The limitation in movement of the arms was not caused by any mechanical obstruction or deformity of the bones.

The patient weighed 127¼ pounds (78.1 Kg.). Her temperature ranged between 98.9 and 99.4 F. The blood pressure was 110 systolic and 70 diastolic. The pulse rate averaged 88 per minute. The thyroid was not palpable, and there was no lymphadenopathy. The heart was normal. The liver and spleen were not palpable. Roentgen examination did not show any pathologic condition of the intestine.

Laboratory examinations revealed that the urine and blood were normal. Chemical studies of the blood showed that the total cholesterol measured 196 mg. per hundred cubic centimeters and the cholesterol esters 147 mg. The blood sedimentation rate, determined by the Westergren method, was only 10 mm. in one hour. The Hinton, Wassermann and Kahn reactions of the blood were negative. The dextrose tolerance test showed a rise to 168 mg. per hundred cubic centimeters of blood in one-half hour, with a drop to 112 mg. in two hours. Practically no sugar was eliminated in the urine during the tolerance test. The Schwartz-McNeil complement fixation test for gonorrhea gave a negative result.

Dr. Charles H. Lawrence, who was consulted, expressed the belief that the endocrine disturbance was due to hypofunction of the ovaries, probably resulting from primary hypofunction of the anterior lobe of the pituitary.

Case 3.—A. P., a brother of the patients in cases 1 and 2, a 31 year old man, stated that he had not previously observed any disturbances of the type present in these persons. The cranial nerves were normal. In sharp contrast to the normal structure of all the other muscles, the flexor and extensor muscles of the upper portions of both arms were markedly underdeveloped, without, however, showing any special weakness. Extension in the elbow joint was not limited. The deep reflexes in the arms were weak. There were no fibrillary twitchings. No sensory disturbances were found. The muscles, as well as the reflexes and the sensibility over the trunk and the lower extremities, were normal.

Cases 4 and 5.—Two sisters of the patients already described were nuns in a convent in Canada, and therefore could not be examined. One, Alma, aged 25, according to her brothers, had a peculiar gait. The other, Anita, aged 21, had difficulty in stretching her arms completely (like the patient in case 1), as well as a peculiar gait.

There were 3 children of patient 1. A summary of their cases follows.

Case 6.—E. P., a 12 year old boy, was able to bend his head. The cranial nerves were normal. However, the "webbed neck" was noticeable, especially on the left side. Both scapulas showed a certain degree of winging, without, however, any definite weakness of the serratus or the trapezius muscles. The patient was able to stretch his arms completely. Like his father, he was unable to bend his vertebral column normally, because the tension of the tendons of the long muscles of the back prevented

complete flexion (fig. 6). Even in a sitting position he was unable to touch his toes with his fingers. Slight weakness of the iliopsoas muscles existed. Although no definite weakness or atrophy of the gluteal muscles could be demonstrated, the waddling gait of the patient was similar to that in cases of progressive muscular dystrophy. The deep reflexes of the legs were weak. There were no sensory changes.

CASE 7.—E. P., a 10 year old girl, had no abnormality except absence of the ankle jerks.

CASE 8.—D. P., a 6 year old boy, like his brother (case 6), had slightly winged scapulas. The cranial nerves were normal. The flexor muscles of the knee joints showed some weakness. The patellar and achilles reflexes were weak.

Fig. 6.—Limitation in bending because of shortening of the muscles of the back.

CASE 9.—The mother of the first 3 patients described was said to have a stiff posture, as well as difficulty in stretching her arms. However, this inability was not as marked as it is in patients 1 and 2. She also complained of pain in the neck.

COMMENT

This is a family in which three generations have exhibited rather characteristic anomalies of the muscles. All the members examined had a short neck and showed limitation of motion in bending the head, both on active and on passive flexion, because of shortening and tension of the neck muscles. Palpation of the cervical portion of the vertebral column did not reveal any anomalies. Roentgen examination

showed that the configuration and the number of vertebrae, as well as the intervertebral disks, were normal. The neck muscles themselves seemed to be normally developed, but were too short. This shortness of the muscles produced the abnormal contour of the neck, which appeared to be shortened and broadened.

The same shortening of the long muscles of the back prevented complete bending forward. The most characteristic manifestation of this disease was shortening of the flexor muscles of the upper portions of the arms. This shortening made complete extension in the elbow joints impossible. Roentgen examination showed that the bones and joints were entirely normal. While the muscles of the neck and back showed normal development and muscular power, the flexors of the upper portions of the arms (as well as the extensors in some members of the family) seemed to exhibit underdevelopment, with a corresponding decrease in muscular power. Two boys of the third generation had somewhat winged scapulas, without, however, any paresis of the shoulder muscles. A certain decrease in the power of the gluteal muscles was also found in some members. Their gait resembled that seen in cases of progressive muscular dystrophy. One member, also, had shortened flexors of the knee joints, with restriction in the full extension of the thighs at the knee joints. Shortness in the calf muscles limited the dorsiflexion of the feet. There were no fibrillary twitchings or change in the electrical response of any of these muscles. The deep reflexes of the upper and the lower extremities were either absent or diminished. There were no pyramidal signs or sensory disturbances. The cranial nerves were intact. The patients did not show any mental or emotional anomalies. The internal organs were normal. One woman, a member of the second generation, had slight endocrine disturbances, which had begun before puberty and were probably the result either of primary or of secondary ovarian hypofunction. Although the patients had had these muscular anomalies since childhood, progressive impairment of function was shown in the case of only 1 member.

The clinical picture presented by members of this family fits none of the well known muscular dystrophies or nervous diseases. We were unable to discover in the literature any description of this type of congenital familial disease.

The shortness of the neck immediately leads one to consider the Klippel-Feil syndrome [1] in differential diagnosis. This congenital mal-

1. Klippel, M., and Feil, A.: Un cas d'absence des vertèbres cervicales avec cage thoracique remontant jusqu'a la base du crâne (cage thoracique cervicale), Nouv. iconog. de la Salpêtrière **25**:223-250, 1912; Anomalie de la colonne vertébrale par absence des vertèbres cervicales. Cage thoracique remontant jusqu'à la base du crâne, Bull. et mém. Soc. anat. de Paris **14**:185, 1912.

formation of the cervical vertebrae is characterized by three main symptoms: (1) absence or shortening of the neck, (2) lowering of the hair line on the back of the neck and (3) limitation of movement of the neck. In a certain percentage of cases of the Klippel-Feil syndrome other symptoms are reported, such as scoliosis or kyphoscoliosis, elevation of the scapulas (Sprengel's deformity), descent of the nipples of the breast, torticollis of muscular or osseous origin and disproportion between the length of the extremities and that of the trunk, giving the patient an almost simian appearance. The following congenital defects may also be observed in rare instances of this syndrome: abnormal dentition; cleft palate; facial asymmetry; deformities of the forearm; clubfoot and clubhand; real defects of the trapezius as well as of other muscles, and vertebral deformities in the dorsal, lumbar and sacral regions.

The main characteristic of the Klippel-Feil syndrome emphasized in all published cases is an incomplete anlage of the cervical vertebrae. Roentgen examination has revealed fusion of the cervical vertebrae into one compact mass. Even those authors (Fischer [2]) who are willing to accept an incomplete form of the Klippel-Feil syndrome agree that anomalies of the cervical portion of the vertebral column must be present for such a diagnosis.

The following nervous symptoms, reported in the published cases of the Klippel-Feil syndrome, must be mentioned because of the anomalies of the muscles and deep reflexes found in the family described here: mental weakness; deaf-mutism; spastic quadriplegia (Guillain and Mollaret,[3] Baruch [4]); syringomyelia (Kallius [5]); anesthesias and paresthesias (Roger, Arnaud and Audier [6]); pseudomyopathy (Sicard and Lermoyez); thenar and hypothenar atrophy (Kallius); cervical spasm, with difficulty in breathing and swallowing (Bauman [7]); hereditary ataxia of the Marie type, or Friedreich's ataxia (Mattirolo and

2. Fischer, H.: Les dysmorphies congénitales du rachis et leurs syndromes cliniques, Paris, Vigot Frères, 1928.

3. Guillain, G., and Mollaret, P.: Syndrome de Klippel-Feil avec quadriplégie spasmodique. Variété étiologique particulière de l'hémiplégie spinale ascendante chronique, Rev. neurol. **1**:436-444 (April) 1931.

4. Baruch, R.: Kongenitale Halswirbelsynostose (Klippel-Feilsches Syndrom) mit spastischer Tetraplegie, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:462-467, 1932.

5. Kallius, H. U.: Die Missbildungen der Halswirbelsäule, insbesondere über das sogennante Klippel-Feilsche Syndrom, Arch. f. orthop. u. Unfall-Chir. **29**:440-466 (May 12) 1931.

6. Roger, H.; Arnaud, M., and Audier, M.: Les manifestations nerveuses du syndrome de Klippel-Feil, Marseille-méd. **1**:233-244 (Feb. 15) 1934.

7. Bauman, G. J.: Absence of the Cervical Spine: Klippel-Feil Syndrome, J. A. M. A. **98**:129-132 (Jan. 9) 1932.

Bertolotti,[8] and mirror movements (Bauman, Willard and Nicholson[9]). We believe that the changes in the deep reflexes in our cases cannot be compared with the nervous disturbances of the Klippel-Feil syndrome.

Certain muscular anomalies have been reported by Bauman,[7] Rœderer,[10] Rechtman and Horwitz[11] and Schinz, Baensch and Friedl.[12] However, all these anomalies are quite different from those observed in the family described. They are the result of abnormalities of the skeleton or the spinal column or of postural defects. In none of these cases was there shortening of the muscles like that observed in the family described.

Familial occurrence, which is rare in cases of the Klippel-Feil syndrome, has been reported by Feil, Bar,[13] Kallius and Sicard and Lermoyez. However, this syndrome is usually not a hereditary anomaly.

The Klippel-Feil syndrome bears some resemblance to the anomaly described in only one respect, the so-called webbed neck. In the Klippel-Feil syndrome this abnormality is caused by malformation of the spinal vertebrae, as previously described. However, changes of the cervical portion of the spine were not found in any member of the family described. Their abnormalities were the result of shortening of the neck muscles. We believe, therefore, that we are justified in eliminating the Klippel-Feil syndrome as the cause of the shortening and the webbing of the neck.

Funke[14] reported a case of an anomaly of the neck produced by a fold extending from the mastoid to the acromion. He designated this condition as pterygium colli. This fold, which was not represented by the trapezius muscle itself, was a fold of the skin formed only by some fibers of the trapezius muscle in its lowest posterior part. The sternocleidomastoid muscle, on the other hand, was found in its upper part. The fold was removed by an operation.

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8. Mattirolo, G., and Bertolotti: Sopra una malformazione rara dell' estremo cefalico della colonna vertebrale. Sindrome di. torace cervicale, Gior. d. r. Acad. di med. di Torino **26**:3-12, 1920.

9. Willard, DeF. P., and Nicholson, J. T.: Klippel-Feil Syndrome, Ann. Surg. **99**:561-567 (April) 1934.

10. Rœderer, C.: Un cas de faux syndrome de Klippel-Feil, Bull. Soc. de pédiat. de Paris **31**:255-261 (June) 1933.

11. Rechtman, A. M., and Horwitz, M. T.: Congenital Synostosis of Cervicothoracic Vertebra (Klippel-Feil Syndrome), Am. J. Roentgenol. **43**:66-73 (Jan.) 1940.

12. Schinz, H. R.; Baensch, W., and Friedl, E.: Lehrbuch der Roentgendiagnostik, Leipzig, Georg Thieme, 1932.

13. Bar, P.: Nouveau-né présentant une sigulière malformation de la colonne vertébral (telescopage vertébral), Bull. Soc. d'obst. de Paris **6**:425, 1903.

14. Funke: Pterygium colli, Deutsche Ztschr. f. Chir. **63**:162-167, 1902.

Funke explained pterygium colli as the result of amniotic adhesions. Kobylinski [15] made a similar observation and concluded that this muscular fold was an atavism, because it is like that found in the chimpanzee. These cases of pterygium colli obviously have nothing in common with those in which the webbed neck is caused by shortening of the muscles of the neck.

Turner [16] described a "syndrome of infantilism, congenital webbed neck and cubitus valgus." He saw 7 patients with a short neck resulting from webbing formation. A winglike fold of skin extended from the mastoid region almost to the acromion. Other symptoms similar to those in the syndrome described were "deformity of the carrying angle of the elbow," cubitus valgus and inability to stretch out the arm entirely. However, shortness of the muscles was not mentioned as a cause of this incapacity. This was so obvious in the cases seen by us that it cannot be disregarded. Turner, in fact, did not emphasize the cause of cubitus valgus but described only such abnormalities as demineralization of the carpal and metacarpal bones, delay in the union of the epiphyses, osteoporosis and lack of calcium. All his patients showed sexual and statural underdevelopment, with definite improvement on the administration of a preparation containing the gonadotropic principle of the anterior lobe of the pituitary. There was no familial correlation, not even in the case of a patient who had a twin sister. Turner claimed that an endocrine disturbance was the etiologic factor in his cases.

Despite some superficial resemblances, there is no doubt that there is no relation between the heredofamilial syndrome of the shortening of the muscles and that described by Turner. In contrast to the cases reported by Turner, there was no endocrine dysfunction in the family described, except in 1 instance.

The heredofamilial character of the syndrome described suggests for differential diagnosis the Werdnig-Hoffmann type of progressive muscular atrophy. However, we believe that the syndrome described cannot be considered as the Werdnig-Hoffmann type of progressive muscular atrophy. The atrophy is too limited. There is no reaction of degeneration, and the process is not progressive to any marked degree. Moreover, shortness of muscles has not been seen in the Werdnig-Hoffmann type of muscular atrophy.

A similarity to the well known symptoms of progressive muscular dystrophy (Erb) is shown in the rather exclusive involvement of the proximal muscles, the weakness of the gluteal muscles and those of the

15. Kobylinski, O.: Ueber eine flughautähnliche Ausbreitung am Halse, Arch. f. Anthrop. **14**:343-348, 1883.

16. Turner, H. H.: A Syndrome of Infantilism, Congenital Webbed Neck, and Cubitus Valgus, Endocrinology **23**:566-574 (Nov.) 1938.

upper portions of the arms and the winged scapulas. However, these findings are not as significant as the shortening of the muscles, which should be considered as the outstanding and leading characteristic. The malformation of muscles observed in some cases of progressive muscular dystrophy appears as an entire defect of a muscle or an anomaly in its structure, but never as a distinct shortening of the muscle. Moreover, the nonprogressive character of the disease described separates it from progressive muscular dystrophy. All these distinctions between the symptom complex of the shortening of the muscles and the already well known types of muscular dystrophies make the assumption of a different form of muscular disease justifiable.

As a result of this study, we believe that the picture presents a heretofore undescribed hereditary familial disease, which appears to affect only the muscular system and is not markedly progressive. However, the nonprogressive character of this anomaly should not be definitely accepted until the patients have been followed for many years. Nevertheless, there is no reason to consider this syndrome as a manifestation of a disease of the spinal cord, since there are none of the characteristic neurologic signs referable either to the anterior horn or to any other part. The absence or the diminution of deep reflexes must not be considered as evidence of a spinal lesion, since this may also occur, for example, in muscular dystrophy.

We do not know whether this disease is as rare as it seems. Perhaps it has not been described because the symptoms are not sufficiently troublesome for the patients to seek medical advice.

SUMMARY

A hereditary familial disease has been described. It is characterized by a short, "webbed" neck as well as by shortness of the neck muscles, long dorsal muscles and flexor muscles of the upper portions of the arms. This shortness prevents the complete bending of the neck and back, as well as the stretching of the arms. There are also underdevelopment and weakness of the proximal muscles of the arms and the gluteal muscles. Decrease in or absence of deep reflexes was found in some members of the family. The webbing, which is formed by the shortened trapezius muscle, causes the neck to appear broader than usual. The cervical portion of the spinal column was normal. Roentgen examination revealed that all the vertebrae were present.

The outstanding symptom of this disease is the shortening of certain muscles. In some cases, some features of progressive muscular dystrophy were present. However, most of the members of this family exhibited mainly shortening and underdevelopment of some muscles. We, therefore, believe that this heredofamilial anomaly is a special type of heredofamilial muscular disease.

CHARACTERISTICS OF AFTER-DISCHARGE FOLLOWING CORTICAL STIMULATION IN THE MONKEY

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Since the discovery of the excitability of the motor cortex by Fritsch and Hitzig in 1870,[1] much interest has been focused on the after-discharges which follow cortical stimulation and which closely resemble jacksonian seizures in man. The present paper is a report of a study of these tonic and clonic after-discharges following cortical stimulation in monkeys, both before and after cortical and subcortical ablations.

METHOD

Forty-seven monkeys—Macaca mulatta, the green monkey (Cercopithecus aethiops sabaeus) or the mangabey (Cercocebus torquatus atys)—were used. Most of the experiments were acute, but in some instances operation was performed under sterile precautions and lesions made which abolished after-discharge at the time. Such animals, when killed nine or ten weeks later, were examined for return of the after-discharge.

The anesthetics used were dial, sodium amytal or ether. Dial was given in doses of 0.45 to 0.50 cc. per kilogram of body weight, half intramuscularly and half intraperitoneally. This produced prolonged anesthesia at a constant depth without unduly depressing the excitability of the motor area (area 4 of Brodmann). It caused marked depression of the premotor area (area 6 of Brodmann), however, and could not be used when this area was to be stimulated. Small supplemental intramuscular doses of either dial or amytal were used to maintain the anesthesia at a constant level for prolonged periods of experimentation.

Sodium amytal was used in a 10 per cent solution, 0.45 to 0.50 cc. per kilogram of body weight, half intramuscularly and half intraperitoneally. It produced a shorter anesthesia, lasting three to four hours, and had the advantage of leaving the premotor area as well as the motor area excitable. Metrazol was used as a stimulant when the anesthesia became too deep.

Ether was used infrequently, and only as a check on observation made on animals under anesthesia induced by one of the other drugs. Under very light ether anesthesia, both the motor and the premotor cortex exhibit as great excitability as it is possible to obtain. It is difficult, however, to maintain a constant level of anesthesia.

From the Laboratory of Physiology, Yale University School of Medicine.

This study was aided by a grant from the Dazian Foundation for Medical Research.

1. Fritsch, G., and Hitzig, E.: Ueber die elektrische Erregbarkeit des Grosshirns, Arch. f. Anat., Physiol. u. wissensch. Med. **37**:300-332, 1870.

The most suitable means of removing cortical areas was found to be gentle suction. An incision was made with a sharp knife into the leptomeninges, and a fine glass sucker under very low pressure was inserted into the opening. It was possible by this means to make exact ablations in a relatively bloodless field, as the pial vessels were not ruptured and the boundaries of the neighboring gyri were not crossed.

All stimulations and ablations were made in the arm area because this was easier to expose than the leg area and because its relations to the central sulcus were more constant. A Wyss stimulator [2] was employed. An effective stimulus for producing clonic after-discharge was found to be one of a frequency of 32 per second (biphasic) with a rising phase of 0.00025 second and a falling phase of four times that duration, applied for five seconds. The peak intensity of the stimulating current was 20 volts, led off from a potentiometer with a maximum resistance of 2,000 ohms. Unipolar stimulation was employed, using an undifferentiated rectal electrode. The chlorinated silver wire of the stimulating electrode was held in place by a dirigible clamp. As a check, an inductorium (1.5 volts in the primary coil) was also used in those experiments in which after an ablation stimulation with the Wyss stimulator failed to produce after-discharge. The results were always the same with the two types of stimuli.

All seizures were recorded mechanically from movements of the affected extremity, usually flexion or extension of the wrist. The arm and forearm were fixed in a wooden block which prevented movement at the elbow, without affecting the blood supply. The arm was counterbalanced by a pulley and a weight in order to maintain the hand on a level with the forearm in the resting position. Finger movements were prevented by strapping the hand to a wooden block. Movements of flexion and extension of the wrist were transmitted by a string through a system of pulleys to a Keith-Lucas lever, which recorded on a kymograph (fig. 1 *A* and *B*).

RESULTS

1. *Relation Between Primary Movement and After-Discharge.*—The characteristics of the primary movements produced by stimulation of the cerebral cortex are too well known to need further description at this time,[3] except for one point conspicuous in our experiments which has direct bearing on after-discharge, namely, that in area 4 more discrete responses are obtained from the regions in the depth of the central sulcus than from the regions on its lateral surface. Thus, for instance, extension of the small finger as well as separate movements of the joints of the fingers and hands was obtained by stimulation of the anterior lip of the central sulcus, whereas stimulation of the external surface resulted always in much larger movements. The threshold for electrical excitability was also always lower within the sulcus than without.

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2. Wyss, O. A. N.: A Condenser Discharge Stimulator for Physiological Purposes, Science **85**:431-432, 1937.

3. (*a*) Bucy, P. C.: Electrical Excitability and Cytoarchitecture of the Premotor Cortex in Monkeys, Arch. Neurol. & Psychiat. **30**:1205-1224 (Dec.) 1933. (*b*) Foerster, O.: The Cerebral Cortex in Man, Lancet **2**:309-312, 1931. (*c*) Vogt, C., and Vogt, O.: Allgemeiner Ergebnisse unsere Hirnforschung, J. f. Psychol. u. Neurol. **25**:273-462, 1919.

Primary movement differed from after-discharge with respect to the following characteristics:

1. Much stronger stimuli were needed to produce after-discharge than primary movement.

2. Primary movement was best produced (with minimal after-discharge) by stimuli of rapidly rising phase. After-discharge (with minimal primary movement) appeared best with longer stimuli of slowly rising phase.

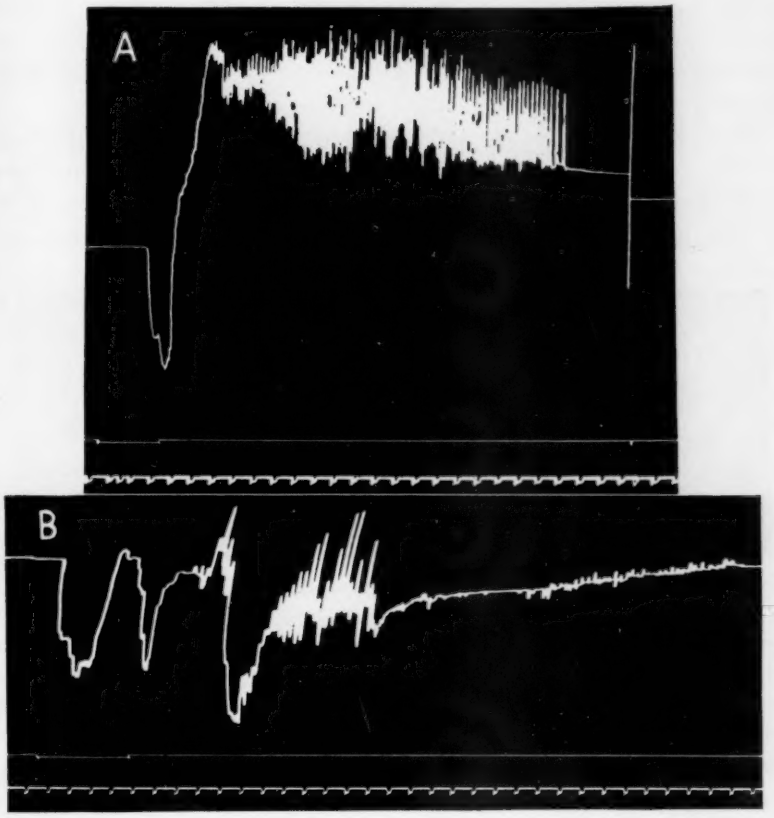

Fig. 1.—*A*, after-discharge in response to stimulation of the flexor point for the wrist in area 4. The early portion of the after-discharge is tonic and associated with extensor rebound. The clonic after-discharge which follows persists for thirty-six seconds. The bottom line records time in two second intervals. The line above it indicates the duration of the stimulus—five seconds in this experiment.

B, complex response to stimulation of area 6. Duration of the stimulus is eight seconds; that of the after-discharge, fifty-eight seconds.

3. Primary movements were specific for the specific cortical areas stimulated, but after-discharges produced by stimulation of many areas of the cortex were indistinguishable from each other in form.

It was possible to observe the clonic movements of after-discharge without any primary movement during the actual period of stimulation. Thus, during stimulation of the leg area no primary movement was visible in the arm. After cessation of the stimulus, after-discharge in the leg spread and became apparent in the arm also. Clonic seizures without primary movement may also appear after stimulation of the postcentral or the premotor area. It is apparent, therefore, that the after-discharge is in no sense a continuation of the original movement.

It was possible also to produce a rapid decrease in the amplitude and duration of the after-discharge while the primary response was slowly increasing in amplitude. In figure 2 it will be noted that after the first stimulus the after-discharge rapidly decreased, while the sub-

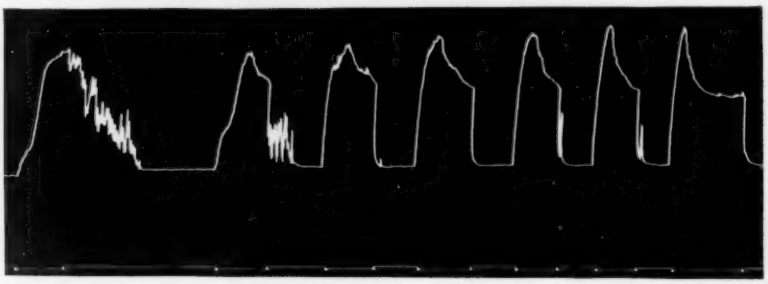

Fig. 2.—Response to repeated stimulation of the extensor point of the motor cortex for the wrist; rapid disappearance of the after-discharge while the primary motor response is increasing in amplitude. The first stimulus is of four seconds' duration.

sequent stimuli at the same point with the same intensity of current caused an increase in amplitude of the primary response.

II. *Effect of After-Discharge on Stability of the Cortical Point.*—Profound physiologic changes were noted in those areas of the cortex which were involved in the spread of activity. It was repeatedly observed that when an extensor point was stimulated after the after-discharge produced by a flexor stimulus, only a flexor response could be obtained. This reversal of an extensor point was more frequently noted than reversal of a flexor point. Figure 3 demonstrates the latter. Graham-Brown and Sherrington [4] and Dusser de Barenne and McCulloch [5]

4. Graham-Brown, T., and Sherrington, C. S.: On the Instability of the Cortical Point, Proc. Roy. Soc., London, s.B **85**:250-277, 1912.

5. Dusser de Barenne, J. G., and McCulloch, W. S.: Factors for Facilitation and Extinction in the Central Nervous System, J. Neurophysiol. **2**:319-355, 1939.

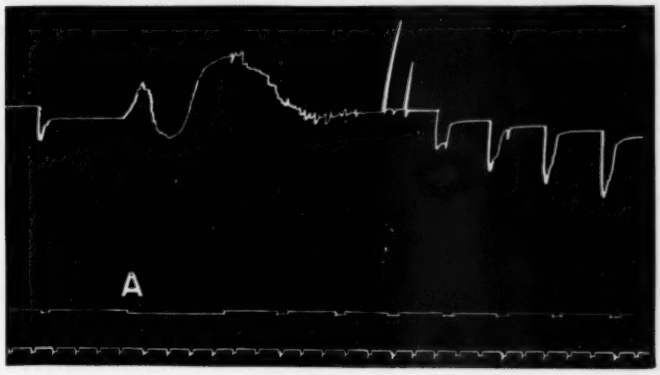

Fig. 3.—Instability of the cortical point following after-discharge. The short, one second stimulations are at the flexor point for the wrist in area 4. The first response is flexor (downward). At *A*, prolonged (eight seconds) stimulation of the extensor point is then followed by after-discharge. The rest of the stimulations are all at the original flexor point. During the after-discharge they have no effect; they are then followed by extensor responses. The flexor response then gradually returns as the effect of the after-discharge from the extensor point wears off.

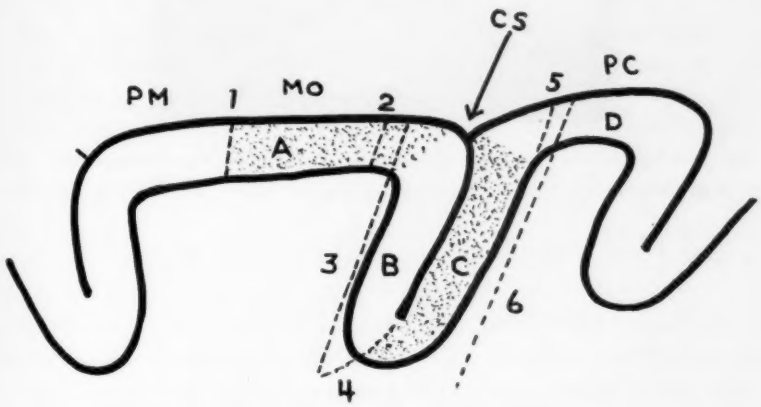

Fig. 4.—Diagram of sagittal section through the arm area of the cortex. *PM* indicates the premotor area; *MO*, the motor area, which is divided into *A*, the exposed portion, and *B*, the anterior lip of the central sulcus; *CS*, the central sulcus; *PC*, the postcentral gyrus; *C*, the posterior lip of the central sulcus, and *D*, the exposed portion of the postcentral sulcus. *1* is a section through the cortex between the motor and the premotor area; *2*, section through the cortex between the exposed portion of the motor area and the anterior lip of the central sulcus; *3*, deep section through the cortex and subcortex, separating the anterior lip of the central sulcus and the exposed portion of the motor area; *4*, undercutting of the anterior lip of the central sulcus; *5*, section through the cortex, separating the posterior lip of the central sulcus from the postcentral gyrus, and *6*, section through the cortex and subcortex, separating the same structures.

reported data on the reversal of cortical points. The phenomenon of extinction, as described by the latter, must have direct bearing on the reversal which follows after-discharge.

III. *Effect of Cortical Ablations on After-Discharge.*—Massive lesions of the cerebral cortex elsewhere than in the precentral gyrus, the postcentral gyrus and area 6 did not cause any changes in after-discharge. Further investigations were therefore restricted to these areas (areas 6, 4, 3, 2 and 1 of Brodmann).

A. Ablations in Precentral and Postcentral Gyri: These regions were divided into four segments (fig. 4): (*A*) the exposed portion of area 4; (*B*) the anterior lip of the central sulcus; (*C*) the posterior lip of the central sulcus, and (*D*) the surface portion of the postcentral gyrus. *A* and *B* together represent area 4; *C* is largely area 3, and

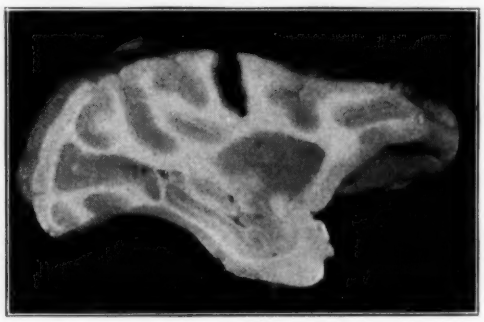

Fig. 5.—Sagittal section showing lesion of the anterior lip of the central sulcus (arm area) which prevents after-discharges and production of discrete movements.

D is areas 1 and 2. If the surface areas, *A* and *D*, were removed, stimulation of the underlying white matter produced typical tonic and clonic after-discharges which were indistinguishable from those obtained from the intact cortex. Ablation of *C* and *D* did not prevent these seizures on stimulation of area 4 or of the exposed white matter of segments *C* and *D*. Extirpation of segment *B*, on the other hand, consistently and permanently prevented the appearance of tonic or clonic after-discharges. Even a small lesion made with an iridectomy knife in this segment consistently prevented any further seizures, no matter what other area of cortex was stimulated (fig. 5).

In several preparations, the anterior lip of the central sulcus was removed under sterile precautions and the animal allowed to survive for over ten weeks. Restimulation at the time of killing produced no clonic after-discharge. In other chronic preparations much larger lesions in segments *A*, *C* and *D* did not abolish after-discharge.

When the white matter beneath the intact cortex of area 4 was stimulated, prolonged after-discharges were regularly observed. But stimulation of the same white matter beneath segment *A* after ablation of segment *B* was followed only by a rapid flexion movement of the arm, which relaxed immediately on cessation of the stimulus. This was the type of response noted by Graham-Brown [6] on direct stimulation of the pyramidal tract in the midbrain following decerebration in the macaque.

After removal of the arm area in the anterior lip of the central sulcus (segment *B*) stimulation of area 6 produced characteristic primary movements, but only the face and leg areas responded with tonic and clonic after-discharges.

B. Ablation of Premotor Area: It has been noted frequently that prolonged tonic and clonic seizures may follow the complicated motor responses elicited by stimulation of the premotor area.[7] However, complete removal of area 6 A did not prevent the appearance of after-discharge from stimulation of the precentral or the postcentral gyrus. A lesion of the cortex which severed the transcortical fibers between areas 4 and 6 and prevented the appearance of discrete movements from stimulation of area 6 [3a] effectively stopped the after-discharges which normally followed stimulation of area 6. In addition, it was possible by specific lesions in area 4 to prevent after-discharge from stimulation of intact area 6. All our experiments, therefore, point to the fact that stimulation of area 6 produces prolonged clonic seizures only by transcortical transmission of impulses to an intact area 4 and that area 6 itself is not necessary for the state of after-discharge.

C. Section of Pathways from the Point of Stimulus to Segment B: The course of impulses traveling from the origin of stimulation to the anterior lip of the central sulcus and producing after-discharge was then investigated by means of various cuts, cortical and subcortical, about these areas (fig. 4): A superficial incision (fig. 4, *1*) in the cortex between areas 4 and 6 prevented after-discharge from stimulation of area 6. A similar superficial incision (*2*) between segments *A* and *B* of area 4 did not prevent seizures after stimulation of segment *A*. After-discharge from stimulation of segment *A*, however, was prevented by a deep incision (*3*) between segments *A* and *B*, but it could still be produced by stimulation of segments *C* and *D*, since the U fibers of the central sulcus were still intact. In the postcentral gyrus, also, sections

6. Graham-Brown, T.: On Postural and Non-Postural Activities of the Midbrain, Proc. Roy. Soc., London, s.B **87**:145-163, 1913-1914.

7. Bucy, P. C.: The Relation of the Premotor Cortex to Motor Activity, J. Nerv. & Ment. Dis. **79**:622-630, 1934; footnote 3a. Foerster.[3b]

must be deep (*6*) before after-discharge from stimulation of segment *D* is prevented.

IV. *Effect of Subcortical Ablations on After-Discharge.*—It was found from the foregoing experiments that the cortex, particularly the anterior lip of the central sulcus, was necessary for the appearance of after-discharge. The next point to determine was whether structures other than the cortex were also necessary.

A. Posterior Roots: The fifth cervical to the first thoracic roots supplying the left arm of a macaque were severed by intradural section. Thereafter, stimulation of the right side of the cortex gave rise to prolonged tonic and clonic after-discharges which differed from those of the preoperative period only in that they were of wider amplitude and of less uniform character. It was obvious, therefore, that the local reflex activity of the spinal cord dependent on tendon and muscle reflexes was not necessary for the development of after-discharge following cortical stimulation.

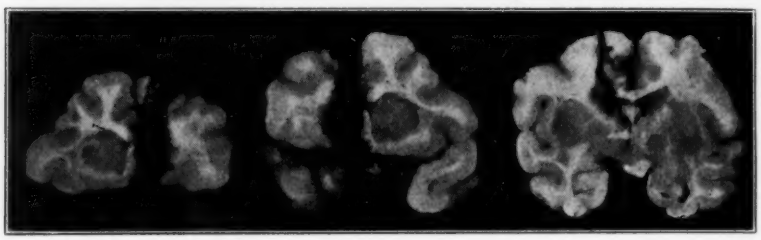

Fig. 6.—Ablation of the head of the right caudate nucleus (serial sections). The first and second sections are contiguous cut surfaces and demonstrate the massive damage to the head of the caudate nucleus as well as to the putamen. This lesion did not diminish the after-discharge from any portion of the sensorimotor cortex.

B. Cerebellum: Resection of this part of the brain did not affect the production of after-discharge following cortical stimulation.

C. Basal Ganglia: The head of the caudate nucleus was destroyed through a lesion in area 6 (fig. 6) without effect on the after-discharge produced a few minutes later by stimulation of area 4. Similar lesions of the globus pallidus and the putamen made through the cortex at the juncture of the sylvian and the rolandic fissure did not prevent after-discharge.

D. Thalamus: According to Dusser de Barenne and McCulloch,[8] the thalamus is necessary for the normal spontaneous activity of the cortex. It has been thought, therefore, that the clonic after-discharge might be

8. McCulloch, W. S., and Dusser de Barenne, J. G.: Functional Interdependence of Sensory Cortex and Thalamus, Am. J. Physiol. **129**:421, 1940.

due to a reverberating circuit between these structures.[5] But the thalamus was destroyed through the postcentral cortex (fig. 7) without any effect on subsequent production of after-discharge.

In the laboratory of Dr. Dusser de Barenne electrocorticograms were taken from 3 preparations in which the cortex was isolated by undercutting from subcortical connections and by splitting the corpus callosum. The typical 3 per second response characteristic of after-discharge appeared under these conditions, as well as in the normal cortex.

COMMENT

Previous studies of electrical activity,[9] hydrogen ion concentration [5] and blood flow [10] have demonstrated that the cerebral cortex is intimately involved in the prolonged clonic and tonic discharges which may follow cortical stimulation. Similar studies have also shown that the seizures are transmitted along the cortex and the immediately subjacent white matter when these are intact. It is certain, however, that tonic and clonic

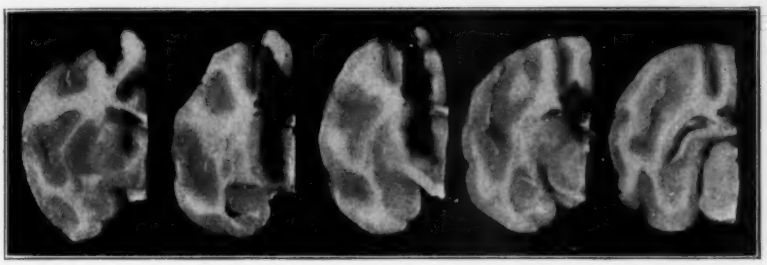

Fig. 7.—Lesion of the right thalamus. A few minutes after this lesion stimulation of the motor area on the same side gave rise to prolonged tonic and clonic after-discharges.

after-discharges are not a property of the cortex alone, for they may appear in the reflex activity of the decerebrate animal.[11] But in man the seizures of jacksonian epilepsy are known to be intimately connected with cortical activity, although it is not known whether the cortex alone is responsible for these tonic and clonic episodes, which have many of

9. Adrian, E. D.: The Spread of Activity in the Cerebral Cortex, J. Physiol. **88**:127-161, 1936. Erickson, T. C.: Spread of Epileptic Discharge, Arch. Neurol. & Psychiat. **43**:429-452 (March) 1940.

10. Penfield, W.; von Santha, K., and Cipriani, A.: Cerebral Blood Flow During Induced Epileptiform Seizures, Human and Mammalian, J. Neurophysiol. **2**:257-267, 1939.

11. Graham-Brown, T.: The Factors in Rhythmic Activity of the Nervous System, Proc. Roy. Soc., London, s.B **85**:278-289, 1912. Sherrington, C. S.: Integrative Action of the Nervous System, New York, Charles Scribner's Sons, 1906, pp. 30 and 228.

the characteristics of after-discharge, as produced by strong electrical cortical stimulation in the experiments described in this paper.

It has been shown in the present series that in the arm area such after-discharges as follow cortical stimulation of area 6 or of the precentral or the postcentral gyrus require the anterior lip of the central sulcus but that they are independent of any subcortical structures. Incomplete studies indicate that the results obtained in the arm area are applicable to the posterior portions of the face and leg centers of area 4 as well.

In the light of the great interest in the neurosurgical treatment of various disturbances of the motor pattern which has developed during recent years, the implications of this study must be considered.

It is interesting that Penfield and Boldrey,[12] in their work on jacksonian epilepsy in human subjects, made the following statement:

> It seems to be a general principle that the discharging state migrates from any particular point upon the cortex toward the Rolandic gyri . . . Thus, an attack which begins at a focus in the parietal lobe does not spread backward into the occipital lobe but forward toward the central fissure.

This is added experimental evidence in support of the concept that the reverberating seizure must, no matter what its origin, reach the anterior lip of the central sulcus before the discharge can take place. Penfield and Boldrey also pointed out that the jacksonian seizures are more easily produced by stimulation at a distance from the central sulcus; this we have also found true of after-discharge in the monkey. It is most easily explained by the concept of a reverberating circuit between the point of stimulation and the anterior lip of the central sulcus.

It has been shown that the anterior lip of the central sulcus in the monkey is the region which integrates the most discrete movements of the fingers and toes. Ablation of this area produces paresis of such movements, but functional recovery following operation is much greater than when the entire arm or leg part of area 4 is extirpated. After-discharges have not been permanently abolished except after removal of the anterior lip, but it is suggested that in surgical therapy for various conditions, the symptoms of which may be due to abnormal conditions of the cortex, ablation of the posterior segment of area 4, and not its entirety, may produce the desired effect of abolition of involuntary motor attacks, with minimal disturbance to voluntary activity.

CONCLUSIONS

The character of the tonic and clonic after-discharges which follow direct cortical stimulation has been investigated in primates, and the following conclusions have been drawn:

12. Penfield, W., and Boldrey, E.: Cortical Spread of Epileptic Discharge and the Conditioning Effect of Habitual Seizures, Am. J. Psychiat. **96**:255-281, 1939.

1. The primary response to stimulation is independent of the after-discharge: Either may be produced alone by appropriate stimuli; the primary response is specific for specific areas stimulated, whereas the after-discharge is not; the nature and strength of the stimulus needed differ in the two instances.

2. After-discharge may be followed by a reversal of direction (flexion or extension) of movement on repeated stimulation of a given point.

3. After-discharge may follow stimulation of the motor area, the premotor area or the postcentral gyrus.

4. Ablation of, or injury to, the anterior lip of the central sulcus of the arm area makes it impossible to produce clonic seizures from stimulation of any other part of the cortex. Ablation of any other part of the cortex is without such effect.

5. Injury or ablation of the following subcortical structures did not significantly alter the amplitude and duration of after-discharge: posterior roots to the affected extremity, the cerebellum, the corpus callosum, the thalamus, the head of the caudate nucleus, the putamen and the globus pallidus.

6. Prolonged after-discharge follows stimulation of the premotor cortex, but a superficial lesion between the motor and the premotor area abolishes this response.

7. The prolonged clonic seizures are the result of a reverberating circuit from the anterior lip of the central sulcus. Its possible pathways are discussed.

ANTICONVULSIVE ACTION OF AZOSULFAMIDE IN PATIENTS WITH EPILEPSY

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The purpose of this study was to continue the investigation of the effects of the anticonvulsive action of certain vital dyes. In 1937 Cobb, Cohen and Ney [1] reported the anticonvulsive action of vital dyes in experimental animals and in patients with epilepsy. Neutral red was demonstrated to have anticonvulsive action in experimental animals and brilliant vital red in both experimental animals and patients with epilepsy. In subsequent reports [2] the first use of disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate (azosulfamide) as an anticonvulsant with epileptic patients was described. This dye, under the name of prontosil S, had previously been reported [3] to be useful in the treatment of infection. Our work has now been carried further, and it is the purpose of this paper to describe its effect on 10 patients with severe epilepsy.

Among the reasons for trying this particular dye on epileptic patients were the following:

1. It is a red dye, as were the other two dyes which were effective.[1] 2. The dye contains an azo linkage and is sulfonated, resembling in those features brilliant vital red. 3. It had been used in patients for other purposes without serious complications.[4] 4. There was suggestive, although by no means conclusive, evidence that paraaminobenzenesulfon-

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1. Cobb, S.; Cohen, M. E., and Ney, J.: Brilliant Vital Red as an Anticonvulsant, Arch. Neurol. & Psychiat. **37**:463 (Feb.) 1937.

2. Cobb, S., and Cohen, M. E.: Neurological Clinic Reports: Cases Presented at the Staff Meetings of the Neurological Service, Massachusetts General Hospital, 1938, p. 115. Cobb, S.; Cohen, M. E., and Ney, J.: Anticonvulsive Action of Vital Dyes, Arch. Neurol. & Psychiat. **40**:1156 (Dec.) 1938.

3. Domagk, G.: Chemotherapie der bakteriellen Infektionen, Angew. Chem. **48**:657, 1935.

4. Colebrook, L., and Kenny, M.: Treatment of Human Puerperal Infections, and of Experimental Infections in Mice, with Prontosil, Lancet **1**:1279, 1936.

amide (sulfanilamide), a related drug, might cause a type of "acidosis," [5] and it is believed that, generally speaking, the "acidotic state" has certain beneficial effects in epilepsy.[6] 5. A preparation of this dye, suitable for oral administration, was available.[7]

METHOD

Ten patients with severe epilepsy of long standing were employed in this study. In 9 cases the purpose of the study was to determine whether the drug caused diminution in the number of the convulsions. The general state of the patient was also observed. In the tenth case the effect of azosulfamide was tested on an epileptic patient with a psychotic state. All the patients were hospitalized during the study, the number of days of hospitalization ranging from twenty-one to three hundred and twenty-five days. The convulsion count was made by the ward nurses. In cases in which the convulsions were slight and the patient's ability to recognize them was uncertain, special nurses were employed to attend the patient constantly during the experimental period. The general method of procedure was to establish a control level for the number of convulsions of each patient; then the drug was given until the level was established for the drug. Then the drug was withdrawn. In some cases placebos, almost identical in appearance with the drug, were substituted. In some instances the nurses, as well as the patient, were unaware of the substitution. In others the procedure outlined had to be modified. For instance, if the patient was too ill to risk establishing a control level of convulsions without medication, a control level was determined with the patient receiving his customary dose of phenobarbital. On two occasions, when the patients lapsed into status epilepticus, phenobarbital was used as an emergency measure. However, it was possible in every case to determine whether the number of the patient's convulsions was less during administration of azosulfamide than during the preceding period and whether the convulsions increased when azosulfamide was withdrawn.

Since leukopenia,[8] anemia [9] and urinary changes [4] had been reported in cases in which drugs of the sulfanilamide family were used, hematologic and urinary studies were made in all cases. The carbon dioxide content [10] and the p_H [11] of the

5. Southworth, H.: Acidosis Associated with the Administration of Para-Amino-Benzene-Sulfonamide (Prontylin), Proc. Soc. Exper. Biol. & Med. **36**: 58, 1937.

6. Lennox, W. G., and Cobb, S.: Epilepsy from the Standpoint of Physiology and Treatment, Medicine **7**:105, 1928.

7. Azosulfamide was supplied for this study by the Winthrop Chemical Co., Inc., New York.

8. Harvey, A. M., and Janeway, C. A.: The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide (Para-Amino-Benzene-Sulfonamide), J. A. M. A. **109**:12 (July 3) 1937.

9. Britton, J. C., and Howkings, J.: Action of Sulfanilamide on Leucocytes, Lancet **2**:718, 1938.

10. Van Slyke, D. D., and Neill, J. M.: The Determinations of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement: I. J. Biol. Chem. **61**:523, 1924.

11. Hastings, A. B., and Sendroy, J., Jr.: Studies of Acidosis: Colorimetric Determination of Blood p_H at Body Temperature Without Buffer Standards, J. Biol. Chem. **61**:695, 1924.

blood were determined in our laboratory; the carbon dioxide–combining power [10] and the chloride [12] and sulfanilamide [13] contents of the blood in the hospital clinical laboratory. A few observations on alveolar carbon dioxide [14] and on minute respiratory volume (by breathing air from the Tissot spirometer) were made. In 2 cases complete studies of acid-base balance were made, with constant diets and analyses of the diet, blood, urine and feces.[15]

The patients also were observed by the usual clinical methods, including history taking, physical examination, roentgenographic study of the skull and electroencephalographic investigation.

PROCEDURES AND RESULTS

Case 1 (fig. 1).—A 13 year old girl who had been having severe convulsive seizures for five years was transferred from a state epileptic colony to this hospital for study. She was maintained on her daily dose of phenobarbital (1½ grains [0.1 Gm.]) for a control period. The dose of phenobarbital was decreased, and the number of convulsions then increased significantly to the level of 5 or 6 per day. Phenobarbital was readministered, and the convulsions again dropped to the usual level of 1 or 2 daily. Again phenobarbital was withdrawn, and again the number of the patient's convulsions rose to 6 per day. This demonstrated that under ordinary circumstances the patient's convulsions would increase if phenobarbital was withdrawn. Azosulfamide was then administered in 5 grain (0.3 Gm.) capsules by mouth, and phenobarbital was withdrawn. The number of convulsions did not rise under this procedure as they had when phenobarbital was withdrawn without use of azosulfamide. Administration of the drug was started slowly, the patient receiving 15 grains (1 Gm.) on the first day and 30 grains (2 Gm.) on the second day, and on the one hundred and nineteenth day of the study, the forty-second day of the administration of azosulfamide, the dose had been increased to 150 grains (10 Gm.) per day. The hemoglobin concentration had dropped during this period from an original level of 91 per cent (Sahli) to 79 per cent. Azosulfamide was withdrawn, and the frequency of the patient's convulsions increased. She became unsteady and uninterested and spoke incoherently. Azosulfamide was readministered, and the number of convulsions again dropped to a lower level and the confusion disappeared.

A placebo capsule was substituted for the azosulfamide capsule after a level was obtained at which the patient had practically no convulsions. Again the number of convulsions rose and the patient's general condition became poor. When azosulfamide was readministered, the number of convulsions again dropped, averaging about 1 per

12. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932, vol. 2, pp. 930-931.

13. Marshall, E. K., Jr.: Determination of Sulfanilamide in Blood and Urine, J. Biol. Chem. **122**:263, 1937. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, ibid. **128**:537, 1939.

14. Boothby, W. M., and Peabody, F. W.: A Comparison of Methods of Obtaining Alveolar Air, Arch. Int. Med. **13**:497 (March) 1914.

15. The mass of data seemed to the editors to be inappropriate for this journal; so it was left out and will be used in a later paper on the chemical pathology. Any especially interested reader can obtain photostats of the tables from us.

ten day period. In addition, it seemed obvious to all observers that the spells were milder and that the patient seemed brighter and more alert. She volunteered the information that she felt much brighter, that she thought she would be able to do better in school, that this medicine did not make her stupid as did phenobarbital. In the latter part of the study, sodium bicarbonate was administered along with the azosulfamide in doses reaching 150 grains (10 Gm.) daily, with no appreciable effect on the convulsive level.

Changes in the chemical constituents of the blood during administration of azosulfamide consisted of a lowering of the carbon dioxide–combining power and a slight increase in chlorides. Hematologic studies showed a drop in hemoglobin concentration from the initial level of 95 per cent to a low point of 62 per cent. From this level it rose to one of 72 per cent, where it was at the time of the patient's discharge (fig. 7). The sulfanilamide level of the blood was about 5 mg. per hundred cubic centimeters. The white cell count fluctuated between 5,000 and 2,000. The red cell count decreased by 1,000,000. It should be stated that twenty-nine

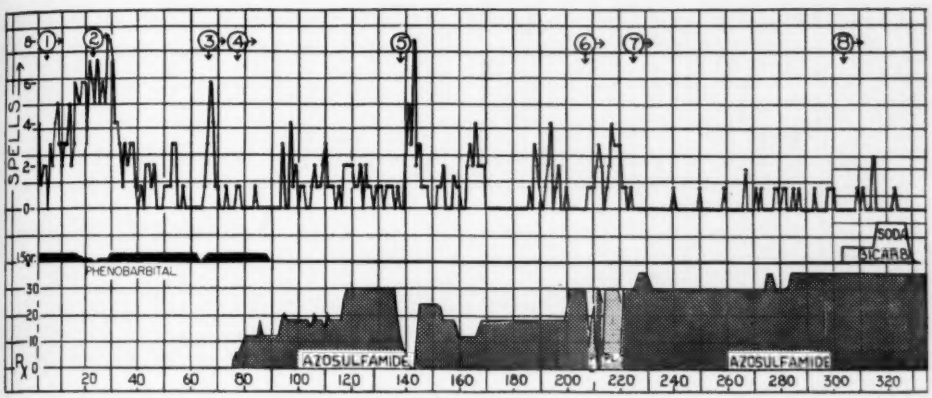

Fig. 1 (case 1).—In this chart and in the subsequent charts, seizures are noted above, the drugs below. Azosulfamide is recorded in capsules (each containing 5 grains [0.3 Gm.]). Other drugs are recorded in units of 1 grain (0.06 Gm.). Time is indicated in days on the abscissas.

The control level of convulsions was established with phenobarbital (*1*). Convulsions increased (*2*) and (*3*) when phenobarbital was reduced in amount.

Azosulfamide (*4*) maintained convulsions at a level lower than the control level.

Azosulfamide was withdrawn at (*5*), and the spells increased markedly. Placebo (*PL*) was substituted for the drug at (*6*). There was coincident increase in convulsions, and the patient became groggy and unresponsive. There was rapid improvement both in the number of convulsions and in the general condition when azosulfamide was readministered (*7*). The addition of sodium bicarbonate (*8*) did not seem to alter the convulsion level.

There was definite anticonvulsive action of azosulfamide in this case.

venipunctures were made on this patient during her stay in the hospital, the blood being taken in amounts ranging from 5 to 50 cc.; this may have contributed to the anemia.

CASE 2 (fig. 2).—A 16 year old girl was transferred from an epileptic colony for study. She had severe epilepsy, with many convulsions, and was feebleminded. When receiving her usual daily dose of phenobarbital, which was 1½ grains (0.065 Gm.), she had about 1 attack per day. The dose of phenobarbital was reduced, and the number of convulsions rose so that on two consecutive days she had 3 severe attacks. She became unsteady and dull mentally. Azosulfamide was administered in doses averaging 150 grains (10 Gm.) per day, and for eight days there were no convulsions; then convulsions reappeared, and there were 4 in a period of thirty-one days. The patient was free of convulsions for eight days; then azosulfamide was omitted. The number of convulsions rose so that on the third day there were 6 violent convulsions (two teeth were knocked out). The patient became comatose and could not be roused between convulsions. A stomach tube was inserted, and 50 grains (3.3 Gm.) of azosulfamide powder dissolved in water was administered. The patient had no more convulsions. Later in the evening

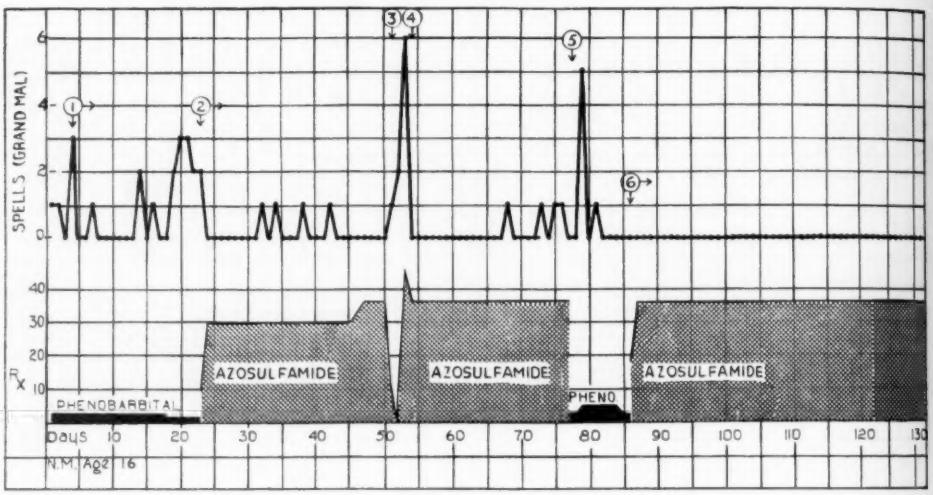

Fig. 2 (case 2).—The patient had, on an average, 1 convulsion daily (*1*) while receiving phenobarbital and 1 to 3 convulsions per day when it was omitted.

Grand mal convulsions decreased (*2*) on administration, on the average, of 30 5 grain capsules of azosulfamide daily. When the drug was omitted (*3*) convulsions increased and the patient was in status epilepticus. Administration of the drug by stomach tube (*4*) during status epilepticus resulted in the patient's recovery, and again the convulsions decreased. Again azosulfamide was withheld, and small doses of phenobarbital were given to prevent too severe an exacerbation. Convulsions again increased; azosulfamide was readministered (*6*), and this time the convulsions were absent for over a month, while the patient was receiving azosulfamide.

In a subsequent period (not shown on the chart) when azosulfamide was omitted convulsions increased. When the azosulfamide was readministered there was definite decrease in convulsions.

There was definite anticonvulsive action of azosulfamide in this case.

75 grains (5 Gm.) and then an additional 75 grains were administered to the patient by mouth. She then resumed regular oral medication, taking 6 tablets

(5 grain) every four hours, or 180 grains (12 Gm.) daily, and was practically free from convulsions.

Azosulfamide was again omitted on the seventy-sixth day of the study in order to observe chemical changes in the blood. Phenobarbital in a dose of 1½ grains (0.1 Gm.) was readministered to avoid return of severe convulsions; despite this, 5 seizures occurred, and the dose of phenobarbital had to be raised to 3 grains (0.2 Gm.) daily. When azosulfamide was readministered she became free of convulsions. Again azosulfamide was omitted and convulsions reappeared, disappearing again when the drug was readministered to the patient.

The hemoglobin concentration dropped from 97 to 83 per cent in the course of the study and the red cell count from 4,500,000 to 3,800,000. During the administration of azosulfamide the carbon dioxide–combining power and the carbon dioxide content of the arterial blood were less than in control periods. The chlorides were higher. The p_H showed no consistent change, but there were more decreased

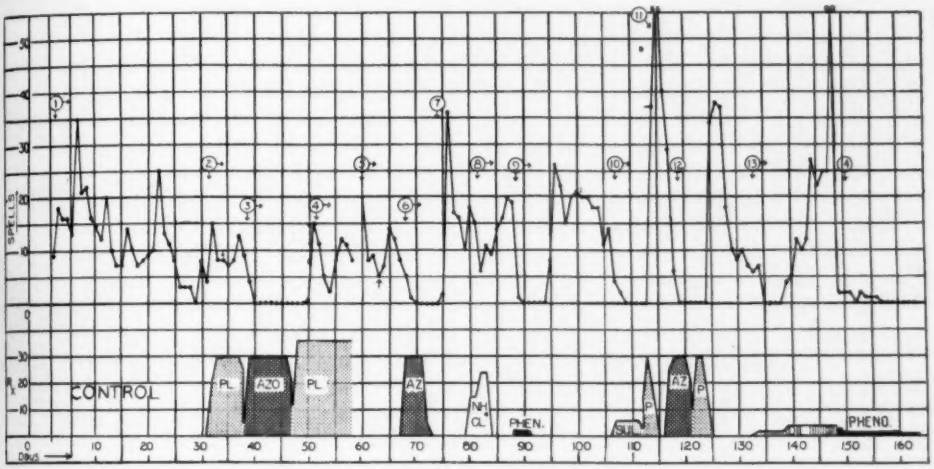

Fig. 3 (case 3).—The patient had many petit mal attacks per day. During the periods of control (*1*) and placebo medication (*2*) the number of spell averaged about 10 per day. There was only one day on which no spells occurred.

With azosulfamide (*3*) the number of spells decreased to a zero level, to reappear when placebo was substituted (*4*) and when no medication was given (*5*).

Azosulfamide was readministered and convulsions again disappeared (*6*), to return (*7*) when azosulfamide was omitted.

Administration of ammonium chloride had no obvious inhibiting effect (*8*), although phenobarbital did (*9*). Sulfanilamide (*10*) inhibited the convulsions; they returned with placebo and disappeared with azosulfamide (*12*). Dilantin (*13*) showed transient inhibiting effect and convulsions disappeared again on administration of phenobarbital (*14*).

There was definite anticonvulsive action of azosulfamide in this case.

values during periods of administration of azosulfamide than during periods in which the patient was without it. The level of sulfanilamide in the blood ranged from 4 to 7 mg. per hundred cubic centimeters.

Case 3 (fig. 3).—A 20 year old girl from the outpatient department of the hospital had suffered many brief lapses of consciousness for twelve years and an

occasional convulsive attack. During a thirty-one day control period the lapses ranged from none to 35 per day, with an average of about 10 per day, there being only one day on which none occurred. Placebo capsules were given, with no diminution in the number. Azosulfamide was then substituted, the dose reaching 150 grains (10 Gm.) daily. On the third day after the beginning of the administration of azosulfamide the number of seizures dropped to zero. There were no seizures for nine days. Placebo capsules were substituted, and on the third day after azosulfamide had been discontinued spells reappeared. Then followed a period when neither azosulfamide or placebo was given, and lapses continued to occur. Azosulfamide was again administered in doses of 150 grains per day, and on the third day of administration the seizures disappeared. When azosulfamide was discontinued the lapses reappeared on the third day after its discontinuation. Ammonium chloride in doses of 75 grains (5 Gm.) for two days and 120 grains (8 Gm.) for two days was given, with no apparent effect on the seizure level. Use of ammonium chloride was discontinued, and the patient was given a four day trial of phenobarbital, 3 grains (0.2 Gm.) daily. Spells disappeared on the third day of administration of phenobarbital and returned on the fourth day after phenobarbital was omitted. With no medication seizures again rose to the previous high level. Sulfanilamide in a dose of 30 grains (2 Gm.) daily was given for a six day period, the dose being halved the last day. There was dropping off of seizures with this drug for a four day period. When placebo was substituted they reappeared. Azosulfamide was given in doses of 150 grains per day, and seizures disappeared for six days. Placebo was given again in the same amounts, and the seizures reappeared the fourth day of its administration. Placebo medication was then discontinued. Dilantin sodium in a dose reaching 4½ grains (0.3 Gm.) was given. There was dropping off of seizures for four days, but they reappeared during the administration of the drug. Phenobarbital was given in a dose of 1½ grains (0.1 Gm.) daily, and seizures disappeared.

The seizure count in this case was kept by the patient. Observation by special nurses and physicians revealed that the patient's count was accurate. Electroencephalographic study showed that all lapses reported by the patient were corroborated by changes in potential commonly seen in cases of petit mal.

The red cell count before administration of azosulfamide was 4,250,000, the hemoglobin concentration 82 per cent and the white cell count 7,000. The chemical changes in the blood under administration of azosulfamide consisted of a decrease in carbon dioxide–combining power, a rise in chlorides, a drop in carbon dioxide content (arterial blood) and a decrease in p_H, as determined by the gasometric method.[16] Complete acid-base balance studies were made on this patient during periods of control and administration of azosulfamide, ammonium chloride and phenobarbital; these will be reported on elsewhere.[16] In the case of this patient it appeared that azosulfamide, sulfanilamide and phenobarbital had an anticonvulsive action. The lack of definite effect with ammonium chloride indicted that if the action of azosulfamide is due to a change in the acid-base balance, the changes are not identical with those of ammonium chloride.

Case 4 (fig. 4).—An 11 year old girl with severe epilepsy was transferred from a state epileptic colony for this study. She had had convulsions for nine years. These seizures were of three types: The first consisted of slight lapses and staring, scarcely perceptible, to be referred to as "lapses"; the second included movements

16. Talbott, J. H.; Coombs, F.; Cobb, S., and Cohen, M. E.: Acid-Base Balance in Epileptic Patients Receiving Azosulfamide, to be published.

of the head, neck, hand and arm, or "slight motor spells," and the third were general (grand mal) convulsions. It was necessary in this case to have observations made by special nurses in order to record accurately the patient's spells. The effect of azosulfamide on the patient's convulsion level was tested by giving the drug and then substituting placebos for it. Azosulfamide was given for eleven days, and a convulsion level was established. Placebo was substituted for three days, and there was an increase in the convulsions and in the number of lapses. Azosulfamide was again given, and the patient's convulsions returned to the former level. On the twenty-third day of the experiment placebo was substituted for seven days, and there was tremendous increase in the frequency of convulsions

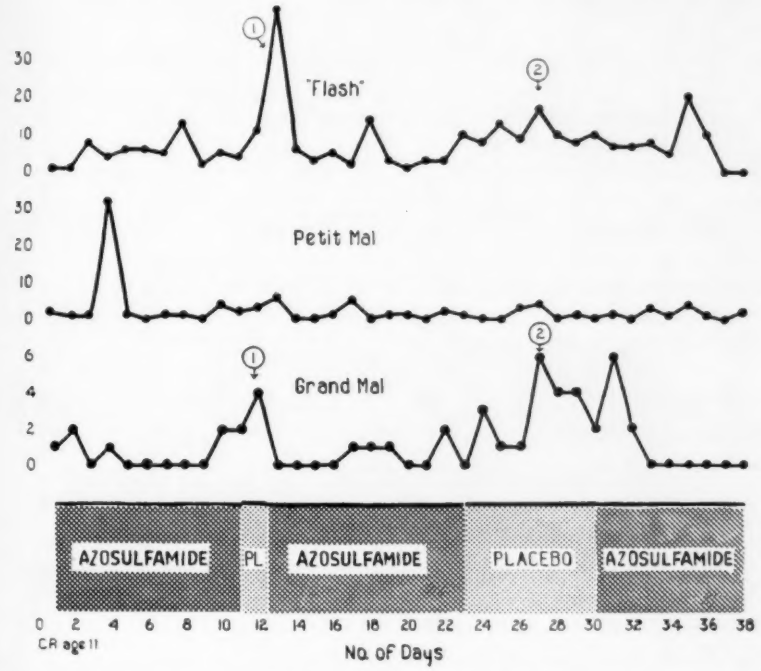

Fig. 4 (case 4).—The number of spells increase in periods (*1*) and (*2*), when placebo was substituted for azosulfamide. This was most marked for the grand mal type.

There was definite anticonvulsive action of azosulfamide in this case.

and of lapses. On the thirtieth day azosulfamide was readministered, and again the number of convulsions diminished.

The initial red cell count was 4,800,000 and the final count 4,100,000; the initial hemoglobin concentration was 95 per cent and the final concentration 85 per cent; the initial white cell count was 5,600 and the final count 6,750. The highest sulfanilamide level in the blood was 7.1 mg. per hundred cubic centimeters.

Case 5 (fig. 5).—A 19 year old girl with severe epilepsy of eighteen years' duration was admitted for study. The convulsions were of two types: general convulsions, and a seizure with staring, impaired consciousness, purposeless move-

ments and falling. The patient was given no medication for the first three days in the hospital, during which time she had 3 severe convulsions; it was decided therefore to start administration of azosulfamide without a control period and to use the effect of withdrawal as a criterion. The dose was at first 150 grains (10 Gm.) and then 180 grains (12 Gm.) daily. When azosulfamide was first administered there were ten days with no spells, which was unusual for the patient, but the attacks reappeared. The dose of azosulfamide was raised and again there was a ten day period free of convulsions. On the thirty-eighth day, however, the patient had 8 convulsions and did not recover completely between them (*2*, fig. 5). Soluble phenobarbital was given intravenously. Administration of azosulfamide was continued; a level of no to 1 convulsion per day was reestablished, and then azosulfamide was omitted. The patient's convulsions rose to 6 per day;

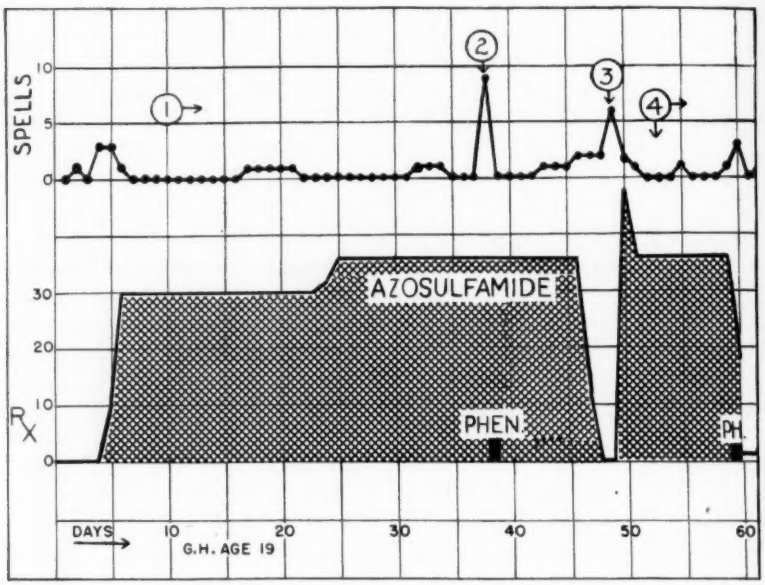

Fig. 5 (case 5).—While receiving azosulfamide (*1*) the patient at first seemed to have fewer convulsions than during the former period (history). However, at (*2*) the patient went into status epilepticus and responded to administration of phenobarbital.

When azosulfamide was withdrawn (*3*) there was immediate marked increase in convulsions, which decreased (*4*) when the drug was readministered.

There was slight, but definite, anticonvulsive response to azosulfamide.

her general condition became critical, and azosulfamide was readministered, with an initial dose of 240 grains (16 Gm.) and then of 180 grains (12 Gm.) daily.

The initial red cell count was 4,600,000, the hemoglobin concentration 87 per cent and the white cell count 6,500. The final red cell count on the eighty-first day of the study was 3,780,000, the hemoglobin content 86 per cent and the white cell count 7,650. The carbon dioxide–combining power (fig. 5) was lower during the period of azosulfamide. The highest level of sulfanilamide in the blood

was 6.1 mg. per hundred cubic centimeters. Determinations of the p_H of the blood revealed no consistent trend.

Case 6.—An 18 year old boy had severe epilepsy, with an average of about 3 to 5 convulsions per day. He was mentally dull. After a control period of nine days, during which the number of convulsions ranged from 1 to 5 daily, azosulfamide was administered in doses of 150 grains (10 Gm.) per day. At first there was a diminution in the number of convulsions, but then they increased. The dose of azosulfamide was increased to 240 grains (16 Gm.) per day. On the eighty-sixth day placebo was administered and was given for four days. On the third day after azosulfamide was withdrawn the number of convulsions rose to 7 per day, and the patient was stuporous or comatose between convulsions. Azosulfamide was then readministered, and in addition oxygen was given, since the patient's condition seemed so poor. After azosulfamide was readministered, the patient's general condition improved, although the number of convulsions did not diminish for seven days. Sulfanilamide was substituted for azosulfamide on the one hundred and thirty-sixth day; 8 Gm. was administered on the one hundred and thirty-seventh day and 12 Gm. on the one hundred and thirty-eighth day. There were no convulsions during that interval, but the patient became stuporous. On resumption of azosulfamide the stuporous condition improved but convulsions continued.

The initial red cell count was 4,880,000 and the hemoglobin concentration 93 per cent. The red cell count on the one hundred and second day of the study was 4,500,000 and the hemoglobin concentration 88 per cent. The highest level of sulfanilamide in the blood during administration of azosulfamide was 6.9 mg. per hundred cubic centimeters, and during the administration of sulfanilamide it was 30.3 mg.

Case 7.—A 22 year old man had an average of 7 lapses a day while outside the hospital under treatment with phenobarbital and dilantin. Azosulfamide was then administered in doses of 180 grains (12 Gm.) daily. On the fourth and the eleventh day of the study the dose was increased to 225 and 230 grains (15 and 15.3 Gm.), respectively. There was no obvious response to administration of azosulfamide. The patient's color became slightly cyanotic, and methylthionine chloride, in doses of from 6 to 12 grains (0.4 to 0.8 Gm.) per day, was added to ascertain whether if the methylthionine chloride relieved the cyanosis of the patient [17] the number of lapses would decrease. No obvious effect was noted. The dose of azosulfamide was decreased on the sixteenth day of the study and omitted on the seventeenth day. On the third day after azosulfamide was omitted, in addition to the lapses the patient had a severe convulsion. On the twentieth day there were 18 lapses.

The initial red cell count was 4,460,000 and the final red cell count 4,410,000. The initial white cell count was 9,300 and the final white cell count 7,300. Determinations of the carbon dioxide content of arterial blood showed a rise after azosulfamide was omitted. The highest level of sulfanilamide in the blood was 3.6 mg. per hundred cubic centimeters.

Case 8.—A 31 year old woman was transferred from a state epileptic colony for study. The duration of her illness was fourteen years. There were three kinds of seizures: lapses (petit mal), general (grand mal) convulsions and

17. Hartmann, A. F.; Perley, A. M., and Burnett, H. L.: Physiologic Effects of Sulfanilamide Methemoglobin Formation and Its Control, J. Clin. Investigation **17**:699, 1938.

seizures in which the left arm stiffened. The patient did not lose consciousness, but stated she was having a spell. She was uncooperative in the study, and it was difficult to evaluate any of the seizures except the general convulsions; so only these were counted. While receiving 4½ grains (0.3 Gm.) of phenobarbital daily the patient had but 1 convulsion in twenty-four days. When phenobarbital was omitted there were convulsions on two consecutive days; the patient's general condition became poor, and administration of phenobarbital was resumed, after which the previous level was established. Azosulfamide was given to the patient in doses of 150 and 180 grains (10 and 12 Gm.) daily. The number of convulsions increased during this period as compared with that for the phenobarbital control period. However, when placebo was substituted for azosulfamide, the number of convulsions rose to a still higher level, reaching 4 per day. Phenobarbital was given again, and convulsions again decreased.

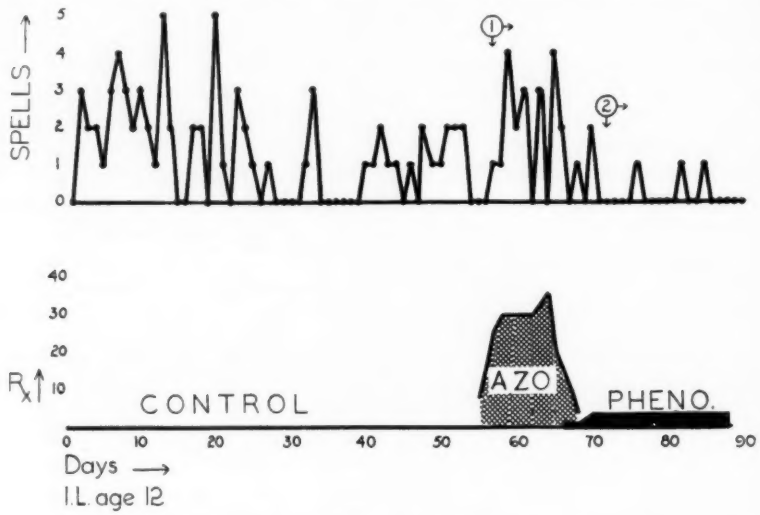

Fig. 6 (case 9).—There was no decrease in convulsions when azosulfamide (*1*) was administered, as there was when phenobarbital (*2*) was given.

There was no anticonvulsive effect of azosulfamide.

The highest level of sulfanilamide in the blood was 6.3 mg. per hundred cubic centimeters. The carbon dioxide–combining power of the venous blood was lower and the chlorides were higher during the period of administration of azosulfamide.

Case 9 (fig. 6).—A 12 year old girl suffering from severe epilepsy of three years' duration was admitted from the outpatient department. Her seizures included general convulsions plus a second type, with staring, aimless movements and falling. During a control period of fifty-four days in which the patient received no medication, the number of seizures ranged from none to 5 per day. On some days there were no seizures. Azosulfamide was given for thirteen days in doses reaching 150 grains (10 Gm.) per day, and there was no decrease in seizures. The drug was therefore discontinued, and phenobarbital, up to 4 grains (0.24 Gm.) per day, was given, with a decrease in the number of convulsions.

On admission the red cell count was 4,480,000, the hemoglobin concentration 98 per cent and the white cell count 9,650. During administration of azosulfamide, the red cell count was 4,450,000, the hemoglobin concentration 91 per cent and the white cell count 9,750. The carbon dioxide content of venous blood diminished during the period of administration of azosulfamide, and the chlorides were slightly increased. There was no consistent change in the p_H of the blood. The highest sulfanilamide level in the blood was 3.6 mg. per hundred cubic centimeters.

CASE 10.—A 24 year old woman who had had convulsions for eleven years began having an increase in convulsions one week post partum. Two weeks post partum a psychotic state developed, with confusion and overactivity, alternating with stupor. During this state 75 grains (5 Gm.) of azosulfamide was administered in one dose, with the intent of discovering whether an immediate, obvious change in mental status would occur. There was no obvious or clearcut response, and the patient's condition did not improve coincident with the administration of the drug.

Summary of Effects of Azosulfamide on Patients with Epilepsy

Case No.	Sex	Age, Years	Weight, Lb.	Average Dose of Azosulfamide, Gr. per Day	Sulfanilamide Level, Mg. per 100 Cc. of Blood	Response to Azosulfamide*
1	F	13	119	150	4.0	+++
2	F	16	111	170	5.0	+++
3	F	20	89	150	2.5	+++
4	F	11	93	150	6.0	++
5	F	19	...	170	4.5	+
6	M	19	130	240	6.0	+
7	M	22	179	180	2.5	+
8	F	31	137	160	5.5	+
9	F	12	131	130	3.0	0
10	F	24	113	75	...	0

* +++ indicates a striking; ++, a moderate; +, a slight, and 0 no response.

SUMMARY OF RESULTS

Ten patients with severe epilepsy were given azosulfamide (table). In 3 patients (cases 1, 2 and 3) there was a marked anticonvulsive effect, and it was possible to repeat the experiment more than once, with similar results, by administering the drug, substituting placebo and readministering the drug. In case 4 the effect was striking, but not to the same extent as that in the first 3 cases. In 4 other cases a slight anticonvulsive effect was shown, but it was not remarkable. In 2 cases (cases 9 and 10) the drug had no obvious effect.

In cases 5, 7 and 8 the apparent anticonvulsive action of the drug was slight, but when the drug was withdrawn there was a marked increase in convulsions. This increase usually occurred on the third day.

In cases 1, 2, 3, 5 and 6 the patients seemed more alert and interested and volunteered the information that they felt less "dopey" during periods of administration of azosulfamide than when they were having no medication or were taking phenobarbital. Such observations are not

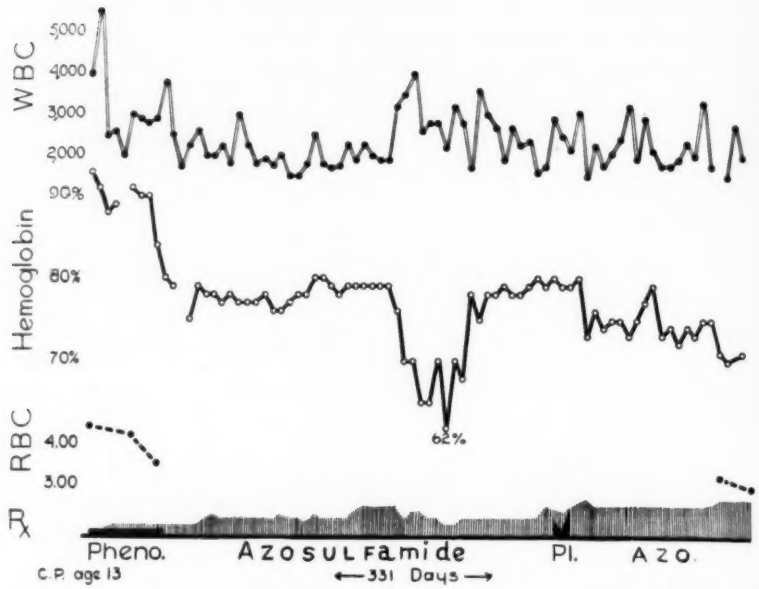

Fig. 7 (case 1).—The patient in this case showed the most marked decrease in the red cell count and the hemoglobin concentration of any patient in the group.

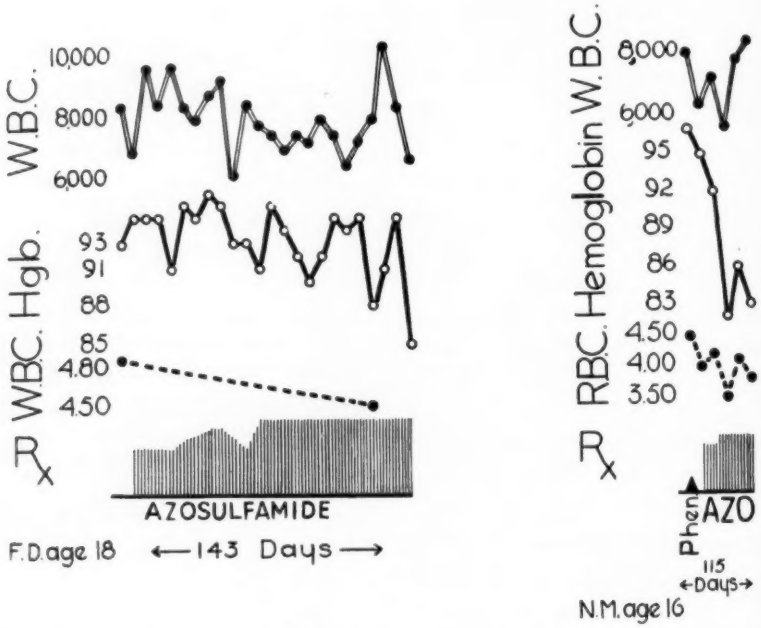

Fig. 8 (cases 6 and 2).—Only a moderate drop in the hemoglobin concentration and the red cell count occurred in these cases.

completely dependable, as they have no quantitative basis, but since the nurses, physicians and patients themselves concurred in this opinion, they seem to be significant.

No special type of convulsion was noted in which azosulfamide demonstrated or failed to demonstrate an anticonvulsive action. Of 3 cases in which anticonvulsive action was shown, typical (grand mal) convulsions occurred in 1 (case 2), many lapses (petit mal) with an occasional convulsion, in another (case 3), and both convulsions and a type of fit characterized by loss of consciousness and groping movements, in the third (case 1).

Studies of the chemical constituents of the blood showed that the average sulfanilamide content ranged from 4 to 6 mg. per hundred cubic centimeters. In most instances, the carbon dioxide–combining power and the carbon dioxide content were lower during the period when azosulfamide was administered and the chlorides were slightly elevated. No obvious trend was exhibited by the p_H. No complications other than anemia were noted in the patients. The lowest hemoglobin concentration, that in case 1, was 62 per cent (Sahli); the lowest red cell and the lowest white cell count, also in case 1, were 2,800,000 and 1,800, respectively (fig. 7). The patient in this case received azosulfamide almost continually for three hundred days, and many samples of blood were taken. On discharge from the hospital the hemoglobin content was 74 per cent. In the other cases the decrease in the blood count was rather slight, as illustrated by figure 8.

COMMENT

Two questions arise from the data presented. First, has anticonvulsive action by azosulfamide been demonstrated in patients with epilepsy? Second, if so, what is the mechanism of this effect?

The method of giving a drug and withdrawing it has certain objections in estimating anticonvulsive action. In this study an attempt was made to rule out the possibility of spontaneous remission by a control period and by noting whether the patient became worse when his usual dose of phenobarbital was omitted. The question of "suggestion" in the treatment of these patients was largely eliminated by the substitution of placebo tablets or capsules for the patient's drug. Under placebo medication the convulsions increased about the third day, a period which corresponds to the time required for the excretion of azosulfamide.[18] Also, the patients had periods when no medication was given, to eliminate the possibility that the placebo was making them worse.

18. Marshall, E. K., Jr.; Emerson, K., Jr.; Cutting, W. C., and Babbitt, D.: Para-Aminobenzenesulfonamide Absorption and Excretion: Method of Determination in Urine and Blood, J. A. M. A. **108**:953 (March 20) 1937.

One has the clinical impression that an increase in convulsions is often followed by a relatively free period. One might wonder whether the apparent response to azosulfamide is simply the consequence to the earlier experiment, in which phenobarbital is withdrawn with increase of convulsions. That this was not the case is demonstrated by the fact that when azosulfamide itself was withdrawn convulsions increased and when it was readministered convulsions diminished. The fact that this could be repeated over and over with the same patient (fig. 3) seemed to rule out the possibility of coincidence.

We believe that the results of these studies do not constitute adequate evidence to establish this drug as an efficient aid in the treatment of epilepsy, although they suggest the possibility. The number of cases here reported is too small to justify generalizations. Whether after long periods of administration the drug would maintain its efficacy and its use remain free of serious complications are matters for further clinical study. Also, no precise information is supplied by this study on optimum dosage, spacing of doses or type of seizure affected. The patients studied here had extremely severe convulsions; the effect of this drug in cases of mild epilepsy is as yet unknown.

It is not clear how azosulfamide works in producing an anticonvulsive effect. That the sulfanilamide fraction may be responsible for some, or all, of the action of the drug is suggested by the fact that in 1 instance (case 3) there was disappearance of petit mal attacks on administration of sulfanilamide, as well as of azosulfamide. Also, in 1 case [19] sulfanilamide was reported to relieve epileptic seizures for two weeks. Rubiazol, a preparation supposedly identical with the original prontosil (4-sulfamido-2',4'-diaminoazobenzene hydrochloride), has also been reported to have anticonvulsive action in three out of four patients.[20] Further investigation will be necessary to determine which fractions of this drug are efficacious and which member of this family of drugs will prove to be most efficient as an anticonvulsant.

We do not know to what extent azosulfamide when given orally, as it was in this study, is absorbed intact as a red dye and to what extent it is broken up. There is controversy as to the exact manner of its absorption and distribution in the tissues.[21] We were unable to demonstrate its presence in either the blood or the spinal fluid. In 1 case in

19. Yeoman, J. C.: Sulfonamide for Epilepsy, Correspondence, Brit. M. J. **2**:261, 1938.

20. Ronchetti, V.: Azione sedatava ed anticonvulsiva dei coloranti azioci caratterizzati dal gruppe sulfamide, Cong. internat. de l'Union thérap. **1**:367, 1937.

21. Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillian Company, 1939.

which autopsy was done (case 6) there was diffuse orange-red staining of the intestines, heart, aorta, kidneys, dura and brain. This suggested, although there was no chemical analysis, that in this case the drug had been absorbed as a red dye. Further study obviously will be necessary to clarify this point. All in all, it seems that most of the evidence points to the conclusion that the sulfanilamide fraction is the important one in producing the anticonvulsive effect.

We have no evidence as to whether the effect is due to "direct" or to "indirect" action on the nervous system. Either or both are possible. Symptoms have been described [22] as being due to direct action of sulfanilamide on the central nervous system.

Of highest interest for speculation is the possibility that the effect produced is due to the property sulfanilamide possesses of inhibiting the action of carbonic anhydrase.[23] This could account for the low carbon dioxide content of the blood, due to its failure to be released from the tissues.

The chemical changes observed in this study coincident with administration of azosulfamide suggested that the acid-base balance might be involved in the production of the anticonvulsive effect. Similar changes, with additional alterations in electrolyte and tissue water balance, have been described.[24] However, no correlation between the number of convulsions on a given day and the values for the chemical constituents of the blood could be established. The method for the determination of the p_H of the blood here employed is not of sufficient precision, we believe, to give the final answer as to possible variations in p_H due to azosulfamide. The chemical studies on these patients were limited, and it was felt that more complete studies on acid-base balance were necessary before further discussion of this aspect could be carried on. Cases 2 and 3 were selected for studies of metabolism and acid-base balance during azosulfamide administration, and the results of these studies will be reported elsewhere.[16]

CONCLUSIONS

1. Azosulfamide has been demonstrated to have anticonvulsive action in some patients with epilepsy.

2. No serious toxic effects were encountered.

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22. Marshall, E. K., Jr.: Bacterial Chemotherapy: The Pharmacology of Sulfanilamide, Physiol. Rev. **19**:240, 1939.

23. Mann, T., and Keilin, D.: Sulphanilamide as Specific Inhibiter of Carbonic Anhydrase, Nature, London **146**:164, 1940. Wood, W. B., Jr., and Favour, C. B.: The Relation of Sulfanilamide "Acidosis" to the Specific Inhibition of Carbonic Anhydrase, J. Clin. Investigation **20**:432, 1941.

24. Beckman, W. W.; Rossmeisl, E. C.; Pettengill, R. B., and Bauer, W.: A Study of the Effects of Sulfanilamide on Acid-Base Metabolism, J. Clin. Investigation **19**:635, 1940.

ABSTRACT OF CASES

CASE 1.—A girl aged 13 had had convulsions for five years. There was a family history of epilepsy and feeblemindedness. She had a history of measles, mumps and an automobile accident with possible fracture of the skull. The present illness was characterized by two types of seizures: a mild type with short loss of consciousness, during which she dropped things, and a more severe one with crying, shaking, loss of consciousness and occasional wetting and tongue biting. The patient had 50 to 100 seizures per month while receiving 1½ grains of phenobarbital daily. Physical examination revealed a scar over the left eyebrow; scoliosis; diminished corneal reflexes; thick speech; increased knee and ankle jerks on the left, and positive Romberg and Chaddock signs.

The electroencephalogram showed abnormal slow waves of high voltage.

The diagnosis was epilepsy (hereditary and traumatic).

CASE 2.—A girl aged 16 had had convulsions for sixteen years. She had a history of whooping cough at three weeks, pneumonia at six months, mumps at 2 years and measles at 3 years of age. She had been having fits on and off since infancy. The first seizure occurred during an attack of whooping cough, at the age of 3 weeks. She "frothed and turned black and rigid." There was only one other attack, between the ages of 3 weeks and 3½ years. Then "choking spells," in which she would fall, began and occurred on the average of 3 to 4 daily. Since she was 8 years old she had had attacks in which "she screamed, her head twisted to the left and her right arm and leg drew up." These usually occurred once a week. On admission to the hospital the patient was having about 2 convulsions a day. Physical examination revealed a scar on the right side of the forehead and carious teeth. There were hyperactive tendon reflexes and unsustained ankle clonus bilaterally. A Chaddock sign was elicited on both sides. The electroencephalogram showed slow waves of high voltage, some of which were flat topped. The ventriculogram revealed displacement of the septum. pellucidum to the right.

The diagnosis was epilepsy (postinfectious).

CASE 3.—A woman aged 20 had convulsions of twelve years' duration. There was a history of mastoidectomy at 4 months, measles and chickenpox at 3 years and pneumonia at 8 years of age. For twelve years the patient has had spells during which she turns "black," her eyes become staring and she does not respond to spoken words. She has had as many as 100 such attacks per day. She has also had convulsions. Physical examination revealed bilaterally diminished corneal reflexes, hyperactive deep tenden reflexes, and a bilateral Hoffmann sign. The hands were cold. Bone conduction was greater than air conduction on the right. The electroencephalogram showed a "wave-spike" pattern.

The diagnosis was epilepsy (possibly postinfectious).

CASE 4.—A girl aged 11 had "fits." The mother had epilepsy. The patient had measles at 5 years of age. At the age of 2 years she had a short period of high fever and repeated convulsions. There were two similar episodes one year and one-half year later. After the third episode, the left side was paralyzed. Since, the patient has had seizures, ranging from none to 15 per day, which vary from slight lapses to convulsions. Speech is thick, and the left side is hemiplegic.

The electroencephalogram showed slow waves of high voltage lasting eight seconds. The pneumoencephalogram revealed dilatation of the right ventricle.

The diagnosis was epilepsy (hereditary, possibly postinfectious).

CASE 5.—A girl aged 19 had had convulsions for eighteen years. She had whooping cough at 1 year and measles, mumps and chickenpox at 4 years of age. Since the age of 1½ years the patient has had convulsions, with generalized clonic movements and biting of the tongue. At 6 years of age another type of seizure developed, in which the eyes remain open and staring and there are inability to respond and groping and clutching movements. The patient may fall or vomit. She has 5 to 6 of these seizures a day when without medication. Bromides reduce the number of seizures but make her duller than usual. On examination the right pupil was slightly greater than the left, but both were large. The hands and feet were moist and cold.

The diagnosis was epilepsy (postinfectious).

CASE 6.—A youth aged 18 had convulsions of six years' duration. A cousin had epilepsy; a maternal aunt, a psychosis. The patient had chickenpox and measles at 7 years, mumps at 9 years and scarlet fever at 12 years of age. After scarlet fever the patient commenced to have convulsions, characterized by a "funny feeling" in the chest, movements of the arm and legs, a dull expression of the face and mumbling speech. Convulsions increased until a level of 1 to 3 per day was reached. Some were followed by a period of unconsciousness. The patient was not helped particularly by various anticonvulsants. Several episodes of status epilepticus occurred. Intelligence gradually diminished.

Physical examination showed the right knee jerk to be greater than the left. Ankle clonus was unsustained bilaterally. A Babinski sign was elicited bilaterally, more often on the left.

The clinical diagnosis was epilepsy (postinfectious encephalitis).

The patient died in status epilepticus.

The diagnosis at autopsy was diffuse cerebral degeneration; meningitis, subacute and chronic; staining of tissues by azosulfamide; marked pulmonary congestion, and healed abscess in the lower lobe of the right lung.

CASE 7.—A man aged 22 had had spells for fourteen years and convulsions for two years. A maternal great aunt was epileptic. The patient had pertussis, mumps and measles in early childhood. Since the age of 8 years, after an operation for hernia with ether anesthesia, the patient began to have spells characterized by brief loss of consciousness and flickering of the eyelids. These would last from five to fifteen seconds. Their frequency had increased from once or twice to five or ten times a day. At 20 years of age the patient had his first convulsion. There have been 7 convulsions since. In these seizures the patient would suddenly jerk the arms and head, then lose consciousness and have a generalized clonic convulsion. The biceps and triceps reflexes and the knee jerk were greater on the left than on the right. The abdominal reflexes on the right were greater than those on the left. The electroencephalogram showed high voltage, slow waves which started in the frontal leads and spread; they were seen in groups of two to eight seconds' duration.

The diagnosis was epilepsy (hereditary).

CASE 8.—A woman aged 31 had had "fits" for fourteen years. She had measles and pertussis at the age or 5 years. One convulsion occurred in infancy. At the age of 17 years the patient started to have short lapses, in which she would stop her present activity for an instant. Since the age of 21 there have been three types of spells: (1) lapses, (2) convulsions, starting in the left leg and the left arm, then involving the opposite extremities and becoming generalized, with loss of consciousness, and (3) falling, with mild twitching of the left

leg and arm and short, or no, lapse of consciousness. The patient averages 7 convulsions per month and from 10 to 80 lapses.

Physical examination showed slight enlargement of the thyroid. A soft systolic murmur was heard over the aortic area; there was slight facial asymmetry; the right pupil was larger than the left; there were questionable weakness of the right side of the face and adiadokokinesis of the left hand; the knee and ankle jerks were greater on the left than on the right. The electroencephalogram showed a few flat-topped, 6 per second waves.

The diagnosis was epilepsy (cause unknown).

CASE 9.—A girl aged 12 had "fits." A paternal aunt was epileptic. The patient had measles and mumps at the age of 7 years. After a cold with cough at the age of 10 years the patient had a generalized convulsion with unconsciousness, lasting three minutes. There were 3 seizures during the next year; then they increased in frequency to 1 or 2 attacks per day. The seizures are of two types: (1) a generalized convulsion and loss of consciousness and (2) spells in which she moves her arms in aimless fashion, does not comprehend and mumbles.

Physical examination showed the face to be asymmetric. The tendon reflexes were more easily elicited on the left than on the right. The pneumoencephalogram was normal. The electroencephalogram showed groups of slow, 2 and 5 per second waves, with increased voltage.

The diagnosis was epilepsy (hereditary, possibly postinfectious).

CASE 10.—A woman aged 24 complained chiefly of confused behavior. She had had an appendectomy. Convulsions had occurred for eleven days, with an average of 1 to 2 per month. Usually there were 7 to 8 lapses on the day following each of these. One year ago there was a transient psychotic episode. One week post partum a series of convulsions occurred, and 2 weeks post partum there developed an episode characterized by overactivity, shouting, confused thinking, mild delusions and disorientation.

Physical examination showed weakness of the right side of the face. The right palpebral fissure was wider than the left. Deep reflexes were exaggerated on the left, with a positive Hoffmann sign. The electroencephalogram showed abnormal, 4 to 5 per second waves, flat topped and of moderate voltage. The diagnosis was epilepsy (cause unknown) with psychotic episodes.

PHYSIOLOGY OF THE SPINAL CORD

I. ROLE OF THE ANTERIOR COLUMN IN HYPERREFLEXIA

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IOWA CITY

In recent years considerable attention has been given to chordotomy in relation to tone and motor function. The idea that dystonic movements and spasticity might be benefited by section of certain tracts in the cord opened an intriguing field of investigation.[1] In studying some 100 patients for whom I have made sections in the cord, I have arrived at certain conclusions concerning the physiology of the cord of man. This paper deals with the results obtained with two types of anterior chordotomy in man—complete and incomplete. The anterior columns were sectioned in one type and preserved in the other. The pyramidal tracts were mildly injured in chordotomies of both types. All the patients had normal motor systems.

COMPLETE ANTERIOR CHORDOTOMY

For a time it was my policy, in attempting to cut the spinothalamic tracts, to make an extensive section in the anterior portion of the cord. The section was begun just anterior to the dentate ligament and carried to the anterior median fissure (fig. 1 *A*). Having established evidence for a more exact location of the pain tracts,[2] I now begin the section about 2 mm. anterior to the dentate ligament and carry it to about 3 mm. mesial to the anterior root (fig. 1 *B*).

In all cases of complete bilateral chordotomy, in which the anterior and anterolateral columns were sectioned, so-called signs of upper motor neuron involvement (hyperactive knee and ankle jerks, patellar and ankle clonus and Babinski's sign) did not develop. The usual postoperative finding was weakness or flaccid paralysis of the lower extremities for several days, followed by complete recovery of normal strength and tone.[3] When voluntary movement returned, there was never inco-

1. Putnam, T. J.: Treatment of Athetosis and Dystonia by Section of Extrapyramidal Motor Tracts, Arch. Neurol. & Psychiat. **29**:504-521 (March) 1933; Treatment of Athetosis by Section of Extrapyramidal Tracts in the Spinal Cord, ibid. **39**:258-275 (Feb.) 1938.

2. Hyndman, O. R., and Van Epps, C.: Possibility of Differential Section of the Spinothalamic Tract: A Clinical and Histologic Study, Arch. Surg. **38**:1036-1053 (June) 1939.

3. "Tone" is used in the sense that patients exhibit good sustained contraction in both flexors and extensors when attempting to resist passive movement. I

(Footnote continued on next page)

ordination or other disturbance of normal movement pattern. The patients first regained good voluntary strength in both flexor and extensor muscles and were able to walk, but tired easily and were unable to maintain contraction for a normal period. Within a month, however, in those who were not too debilitated from carcinoma, it was difficult to detect any objective abnormality in the motor system.

In many of these chordotomies the pyramidal tracts were undoubtedly partly injured, if only by transient edema, but nevertheless the expected signs of upper motor neuron involvement did not develop.

The following case will serve as a typical example of complete anterior chordotomy. The man was the first patient with gastric crises for whom I performed a bilateral chordotomy; being anxious to make a thorough section, I cut the entire anterior half of the cord, preserving the anterior spinal artery (fig. 1 *A*). The case, reported only in abstract here, has been described in greater detail in another paper.[4]

J. J., a white man aged 38, for four years suffered severe attacks of acute abdominal pain and vomiting. The attacks increased in frequency until they occurred daily. He was unable to take food and had lost 35 pounds (15.9 Kg.) in weight in ten months. A long course of antisyphilitic therapy had apparently arrested the progress of the disease, though the Wassermann reactions of the blood and spinal fluid were positive. Aside from Argyll Robertson pupils, the neurologic examination gave essentially negative results. The motor and the sensory status were carefully noted by Dr. Clarence Van Epps, of the department of neurology, as well as by me.

Operation.—Bilateral chordotomy was done at the third dorsal segment, the levels of the sections being slightly different (fig. 1 *A*).

Postoperative Course.—The gastric crises, including pain and vomiting, have not recurred up to the time of writing (three years). Discrimination of pain and temperature was abolished from the fifth dorsal segment down.

For five days, including the day of operation, the patient was unable to move his legs. On the sixth day voluntary function began to return and progressed gradually to 100 per cent recovery. During the first five days the paraplegia was of flaccid type with complete absence of all reflexes, including flexion reflexes. On the seventh day a 1 plus knee jerk response was present bilaterally and developed gradually to a 2 plus (the preoperative estimate) by the twenty-fourth day. The achilles tendon reflex made its feeble appearance several days after the return of the knee jerk and developed to a 1 plus reaction by the twenty-fourth day. Response to plantar stimulation appeared after the return of the

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feel that the following observation is worth recording, however. When one makes the usual tests for flexor and extensor strength of the toes, ankles, legs and thighs while the patient lies in bed, the results may be recorded as 100 per cent. When the patient attempts to walk, however, he appears to have a subjective feeling of insecurity at the knees. It has required one to six months in some cases for this sense of insecurity to disappear. In some cases it has persisted for more than a year after section of the anterior columns.

4. Hyndman, O. R., and Jarvis, F. J.: Gastric Crisis of Tabes Dorsalis: Treatment by Anterior Chordotomy in Eight Cases, Arch. Surg. **40**:997-1013 (May) 1940.

ankle jerk and was of normal plantar type by the twenty-fourth day. There has never been the slightest semblance of upper motor neuron signs—extensor spasticity, hyperactive deep reflexes, dorsiflexion of the great toe or ankle or patellar clonus. Voluntary control of the bowels and bladder was lost for about sixteen days, then gradually returned to normal.

One month after operation the flexor and extensor strength of the legs was 100 per cent. During the recovery there was not the slightest evidence of asynergia, ataxia, incoordination or tremor. The heel to knee and toe to finger

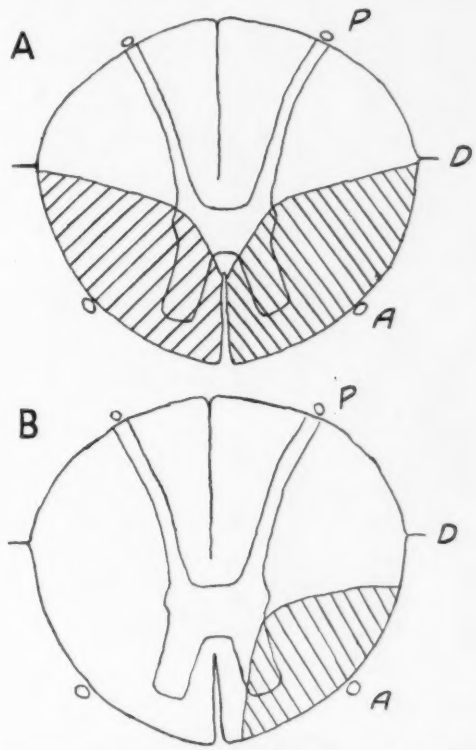

Fig. 1.—*A*, diagram to illustrate the manner in which I did the first chordotomy for relief of gastric crises. A number of my earlier chordotomies were done in this way, and I have referred to them as complete anterior chordotomy. The anterior columns, in addition to other tracts, are destroyed by this section, and it is presumable that the pyramidal tracts are at least partly injured.

B, diagram to illustrate manner in which chordotomy is now done to effect complete interruption of the spinothalamic tract with a minimal section

In this figure and in figure 3, *P* indicates posterior root; *D*, dentate ligament, and *A*, anterior root.

tests were normally performed. In short, when motor activity became possible, there was never any disturbance in the pattern.

In the early postoperative days it was obvious on palpation that the muscles of the thighs and calves were soft and flabby. At the time the patient was dis-

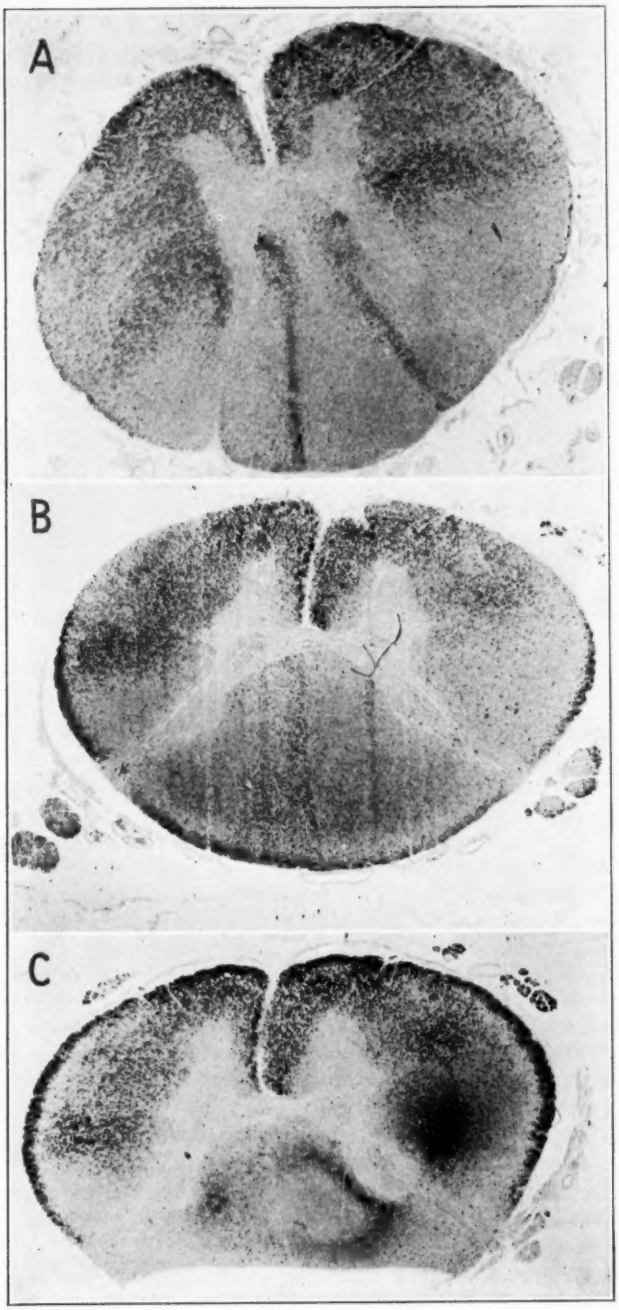

Figure 2

(See legend on opposite page)

charged (the twenty-ninth postoperative day) he was walking and performing in all respects with normal movement pattern, but was easily fatigued. A walk of twenty steps caused him to perspire from fatigue.

Follow-Up Examination.—Six months after operation he appeared healthy, with no complaints, and was contented, ambitious and grateful. He had been working full time at his trade, carpentry and mechanics. He was able to work on and around scaffolding with ease. He had gained 25 pounds (11.3 Kg.) and had full control of the bowels and bladder. Tone and motor function of the lower extremities were normal in all routine tests.

Evidence That Complete Anterior Chordotomy as Performed Damages the Pyramidal Tracts to Some Extent.—I have performed complete anterior chordotomy on 3 patients who, because of severe metastatic carcinoma, died in less than a month after operation.

F. K., a woman of 46, underwent chordotomy on July 8, 1937 for relief of pain due to a carcinoma of the cervix with metastases to the viscera and lungs. After operation the ankle and knee jerks returned to a slight degree, and she could flex and extend the legs and ankles with fair strength. She died on the eighth postoperative day, and a Marchi preparation was made of a section of the cord below the lesion (fig. 2*A*).

H. S., a man of 24, had a chordotomy on May 28, 1938 because of pain due to an adenocarcinoma of the rectum with metastases. Motor function was retained in the lower extremities, but was about 50 per cent of normal. He died on the sixteenth postoperative day, and a Marchi preparation was made of a section of the cord below the lesion (fig. 2*B*).

W. J., a man of 68, had a chordotomy on Feb. 17, 1939 for relief of pain from a hypernephroma which had metastasized to the first lumbar vertebra. After operation the ankle and knee jerks and the plantar response did not reappear, though they had been normally present before operation. He was able to flex and extend his legs, though they were weak. He died twenty-five days after operation, and a Marchi preparation was made of a section of the cord below the lesion (fig. 2*C*).

After operation all 3 of these patients had some motor function of the lower extremities and normal sensation except for impaired sensibility to pain and temperature. There was not the slightest evidence

EXPLANATION OF FIGURE 2

Fig. 2.—*A,* Marchi preparation of the cord of patient W. J., showing descending degeneration of the anterior columns and some degeneration of the pyramidal tracts, especially on the left.

B, Marchi preparation of the cord of patient H. S., showing descending degeneration of the anterior columns and some degeneration of the pyramidal tract on the left.

C, Marchi preparation of the cord of patient F. K., showing descending degeneration of the anterior columns and some degeneration of the pyramidal tracts, particularly on the left side. The spots in the right posterior column and in the right pyramidal tract are artefacts.

of hyperactive reflexes, clonus or plantar extension of the great toe. The lower extremities were not spastic. All 3 of the patients lived long enough and were in sufficiently good condition for a time after operation for signs of upper motor neuron damage to have developed if the necessary neural mechanism had not been interrupted. Ankle clonus and plantar extension of the great toe may appear within a few hours after an injury to the pyramidal tract, and in the 5 patients referred to under "Partial Anterior Chordotomy," in whom the anterior columns were spared, these two signs, in addition to hyperactive deep reflexes, were present the day after operation. The Marchi preparations of sections of the cord from the 3 patients just discussed demonstrate degeneration of the anterior columns and also definite injury of the pyramidal tracts.

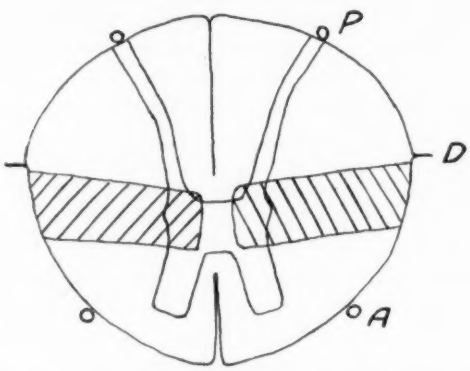

Fig. 3.—Diagram to illustrate the manner in which a chordotomy was done in 5 patients. An attempt was made to destroy sympathetic function in the cord by section at the third thoracic segment as treatment for essential hypertension of advanced grade. This type of section has the same probability of at least partly injuring the pyramidal tracts as has the section illustrated by figure 1 *A*. The anterior columns in this section, however, were spared.

PARTIAL ANTERIOR CHORDOTOMY

In carrying out a new surgical approach to the problem of treatment of essential hypertension, I have recently sectioned the supposed region of the sympathetic tracts in the cord.[5] Six patients have been

5. The results of this method will be submitted for publication at a later date. The sections evidently did not completely interrupt the sympathetic tracts, since the thermoregulatory sweating test resulted in normal sweating after operation, except in 1 patient (Hyndman, O. R., and Wolkin, J.: Sweat Mechanism in Man: Study of Distribution of Sweat Fibers from the Sympathetic Ganglia, Spinal Roots, Spinal Cord and Common Carotid Artery, Arch. Neurol. & Psychiat. **45:** 446-467 [March] 1941).

so treated. Sections were made bilaterally in the cord at the third thoracic segment, in the manner indicated in figure 3.

The posterior aspect of the spinothalamic tract was variously injured by this section, so as to be followed by loss of cutaneous sensibility to pain and temperature to the knees, or even as high as the pelvis. These results are in keeping with the views expressed in a recent publication.[2] The anterior columns were spared. Five of the 6 patients on the day following operation presented hyperactive knee and ankle jerks, ankle clonus and extension of the great toe on stroking the sole of the foot.[6] These signs have remained to the time of writing (eight to twenty-four months), though they have tended to become somewhat less active, particularly the clonus. Extensor spasticity did not develop except in 1 patient, who only at times exhibited mild resistance to flexion of the knee.[7] The absence of spasticity, in my opinion, is due to the fact that injury to the pyramidal tracts was not extensive, although Tower's [8] recent work on monkeys indicates that section of the pyramidal tracts is not followed by extensor spasticity or other "release" signs. The neurologic picture following a limited section of this kind is entirely different from that following a complete section, such as that indicated in figure 1 *A*.

I can account for these results of limited chordotomy only by assuming that the pyramidal tracts were partially injured and that the extrapyramidal tracts in the anterior columns remained intact. It is assumed that the mild damage to the pyramidal tracts was similar in the two types of chordotomy (complete and partial) inasmuch as the posterior aspect of the incision was the same in both cases. The essential difference in the two incisions is that the partial chordotomy spares the anterior columns and part of the anterolateral columns. The term pyramidal tract is used in a topographic sense, it being recognized that the tract may contain fibers from the premotor as well as from the motor cortex. The pyramidal tracts were not sufficiently injured to prevent the patients from subsequently walking alone.

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6. In the sixth patient I made the section at a level slightly anterior to that in the other patients. This was done purposely in an attempt to avoid injury to the pyramidal tracts. Thus it is quite likely that the pyramidal tracts were not injured. The motor status of the lower extremities of this patient was not changed after operation.

7. Bergmark (Brain **32**:342-477, 1909-1910) called attention to the fact that excessive reflexes may occur without hypertonus being present or before it has had time to develop. Although the time at which reflex hyperexcitability develops in hemiplegia varies considerably, according to Monakow and Oppenheim it appears as soon as the patient wakes up from the comatose state.

8. Tower, S. S.: Pyramidal Lesion in the Monkey, Tr. Am. Neurol. A. **64**: 95-101, 1938.

COMMENT

What role do the extrapyramidal tracts play in man? I have given evidence that they are not indispensable to normal reflexes and movement patterns and that their loss is in no way comparable to the loss of the nuclear structures from which they arise.[9] A transient period of flaccid paralysis following complete section of the anterior half of the cord may indicate a minor role of the descending extrapyramidal tracts. The return of normal function, however, would lead to the supposition that the pyramidal tracts may serve as the final common path from the brain to the cord for normal motor activity. Likewise, in consideration of the present state of knowledge of neuroanatomy, it follows that the final expression from the cerebellum and the striatum, and indeed from all the basal ganglia, can relate functionally with the cortex.[10] The probability also follows that in cases of striatal deficiency disease anterior chordotomy would fail to impoverish the dystonic motor phenomena—certainly to a degree that might at first have been expected. If the pyramidal tracts are left intact, motor function with its previous disorders should return.

It appears that in man the posterior columns and pyramidal tracts have superseded almost completely the extrapyramidal tracts in the anterior part of the cord, but in the event that the pyramidal tracts are destroyed, the prespinal system (with descending extrapyramidal tracts) is released and is responsible for the acute development of hyperactive deep reflexes, clonus and the Babinski sign. It may be recalled that the extrapyramidal tracts (vestibulospinal) are also necessary to the decerebrate state.[11]

If the pyramidal tract sustains a mild injury and the anterior columns are intact, hyperactive deep reflexes, clonus and the Babinski sign will develop immediately or within twelve to twenty-four hours. If the anterior columns are severed these signs will not develop, even in the chronic state. The signs do develop in spinal man after a long period, but in this case the pyramidal tracts are completely interrupted. In any event, the anterior columns are essential to the acute development of the signs and to their development after mild injuries of the pyramidal tracts.

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9. Putnam [1] has remarked on the absence of permanent disability following a section of the descending extrapyramidal tracts.

10. In this discussion I wish to avoid the implication that area 4 is the sole origin of the pyramidal bundle.

11. Sherrington, C. S.: Decerebrate Rigidity and Reflex Co-Ordination of Movements, J. Physiol. **22**:319, 1897-1898. Fulton, J. F.; Liddell, E. G. T., and Rioch, D. M.: The Influence of Unilateral Destruction of the Vestibular Nuclei upon Posture and the Knee Jerk, Brain **53**:311-326 (Oct.) 1930.

CONCLUSIONS

Section of the anterior half [12] of the cord results at most in transient flaccid paralysis and a longer-lasting loss of extensor tone or sustained antigravity reflex.

The descending extrapyramidal tracts, and in fact the anterior half of the cord, are not indispensable to normal strength and movement patterns in man. The tracts in the anterior columns do appear to contribute to the sustained contraction of the antigravity muscles, such as is necessary in standing and walking. The loss of strength which follows anterior chordotomy is a subjective complaint rather than an objective finding.

When the anterior half of the cord was divided, upper motor neuron signs, which characterized lesions of the pyramidal tract, did not appear during the period of observation, up to three years. It is assumed that in performing this type of chordotomy the pyramidal tracts, at least in some patients, were damaged sufficiently to have resulted in the upper motor neuron signs had the neural mechanism necessary for their development not been interrupted.

A mild injury of the pyramidal tracts with preservation of the anterior columns is followed by acute development of hyperreflexia—hyperactive knee and ankle reflexes, ankle clonus and a Babinski sign. Involuntary resistance to flexion and extension of the foot and leg (spasticity) does not supervene.

Hence hyperreflexia may obtain independent of spasticity.

The acute development of hyperreflexia with the anterior columns intact, in contradistinction to chronic development of hyperreflexia in spinal man, indicates a dual mechanism for so-called upper motor neuron signs. One mechanism operates through the agency of the anterior column, while the other is a purely spinal phenomenon.

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12. By anterior half of the cord is meant that portion indicated in figure 1 *A*. It would be difficult to estimate at present the significance of the uncrossed corticospinal fibers in the anterior columns.

CEREBRAL ARTERIOGRAPHY

ITS PLACE IN NEUROLOGIC DIAGNOSIS

SIDNEY W. GROSS, M.D.
NEW YORK

Cerebral arteriography has not been widely employed in this country, and its value as an important adjunct to neurologic diagnosis has not been generally appreciated. The technic for the visualization of the vascular supply of the brain was introduced by Egas Moniz [1] in 1927. After experimenting with several radiopaque substances, Moniz finally advocated the injection of a colloidal preparation of thorium dioxide (thorotrast). This method has been used extensively by its originator and has also found favor in several European clinics. The objections to cerebral arteriography and its relative neglect by American neurosurgeons are due to the toxicity and potential hazards inherent in the use of thorium compounds. Abundant evidence is available that thorium compounds are radioactive.[2] Martland [3] stated, "The routine use of thorium dioxide sol is criminal."

These substances may be injected into the vascular system or the body cavities with but slight immediate reaction. However, once introduced, they are not excreted, but the particles of radioactive thorium compounds are deposited in the reticuloendothelial system, where they remain indefinitely. The tendency for thorium compounds to produce necrotic and malignant changes in tissues is well known. Recently, cerebral injuries attributed to the use of thorium dioxide in arteriography were reported by Ekström and Lindgren.[4] They studied the brains obtained from 35 patients on whom arteriographic studies with thorium dioxide had been made in Olivecrona's clinic. In 21 patients thorium was demonstrated histologically in the intravascular tissues. In 6 multiple injuries in the cerebral parenchyma due to occlusion of small

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From the Mount Sinai Hospital.

1. Egas Moniz: L'angiographie cérébrale, Paris, Masson & Cie, 1934.

2. Northfield, D. W. C., and Russell, R. S.: Fate of Thorium Dioxide in Cerebral Arteriography, Lancet **1**:377, 1937. Potential Hazards of the Diagnostic Use of Thorium Dioxide, editorial, J. A. M. A. **108**:1656 (May 8) 1937. Biskind, M.: Drug & Therap. Survey **1**:21 1938.

3. Martland, H. S., in Cecil, R. L.: Textbook of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1937, p. 551.

4. Ekström, G., and Lindgren, A. G. H.: Cerebral Injuries After Arteriography of the Brain with Thorotrast, Acta chir. Scandinav. **82**:291-302, 1939.

vessels by thorium dioxide were found. These investigators concluded that the injection of thorium dioxide was an important contributory factor in the death of several of the patients in this group. Hemiplegia and other focal cerebral disturbances have occurred immediately after the injection of thorium dioxide.

For several years various workers have searched for a relatively safe, rapidly excreted substance for visualization of the cerebral blood vessels. Preliminary reports of my work with diodrast have been published.[5] The technic has been more or less standardized and has now been employed with a sufficient number of patients to warrant further use.

The pharmacologic properties and chemical composition of diodrast (3,5-diiodo-4-pyridon-N-acetic acid diethanolamine) are well known. It has been used for many years as a roentgenographic agent in intravenous urography and more recently by Robb and Steinberg[6] for the visualization of the chambers of the heart, pulmonary circulation and great blood vessels in man.

Diodrast is relatively nontoxic in the quantities used, except for persons who have an idiosyncrasy for iodine compounds. It is excreted rapidly by the kidneys, largely, if not completely, unchanged.

CEREBRAL ARTERIOGRAPHIC TECHNIC

The cerebral arteriographic technic with the use of diodrast has been described.[7] The patient is prepared by the hypodermic administration of 5 grains (0.3 Gm.) of soluble phenobarbital about thirty minutes before the examination. Exposure of the common carotid artery is carried out with the use of local anesthesia by means of a small incision just above the clavicle and parallel to it. Using a 17 gage curved needle to which a rubber tubing connection is attached, the lumen of the common carotid artery is penetrated, and 10 to 12 cc. of a warm 50 per cent solution of diodrast is rapidly injected (fig. 1). A roentgen film of the skull is quickly exposed (for one-fourth to three-eighths second) during the injection.

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5. Gross, S. W.: Cerebral Arteriography in the Dog and in Man with a Rapidly Excreted Organic Iodide, Proc. Soc. Exper. Biol. & Med. **42**:258-259, 1939; Cerebral Arteriography by Means of a Rapidly Excreted Organic Iodide, Arch. Neurol. & Psychiat. **44**:217-222 (July) 1940.

6. Robb, G. P., and Steinberg, I.: Visualization of the Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Man, Am. J. Roentgenol. **41**:1-17, 1939.

7. Gross, S. W.: Cerebral Arteriography with 50 Per Cent Diodrast, Radiology, to be published.

In the early cases a 70 per cent solution of diodrast was injected. However, 3 of 12 patients given such injections had immediate jacksonian seizures. A 35 per cent solution of diodrast was then tried. This concentration proved safe and has also been used in cerebral arteriography by Pool and by Torkildsen. However, in our hands satisfactory roentgenograms were not always obtained with a 35 per cent solution. A 50 per cent solution of diodrast has now been employed in 10 cases. So far a jacksonian seizure, lasting forty seconds, has occurred in only 1 case. In this case it is probable that the convulsion was due to the injection of an excessive quantity of the solution.

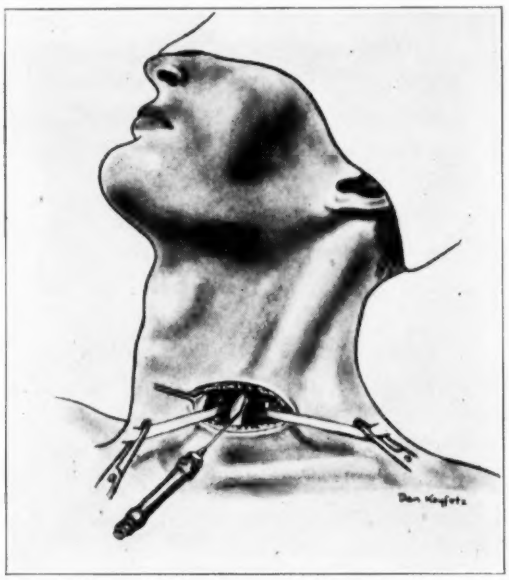


Fig. 1.—Cannula inserted into the common carotid artery.

THE NORMAL ARTERIOGRAM

The number of arteriographic examinations which have been performed is now sufficiently large for the normal arteriogram to be fairly well known. Egas Moniz [1] and Turnbull [8] have published good examples of the normal arteriogram. Figure 2 is a diagrammatic representation of such an arteriogram. While variations in size, configuration and distribution of the blood vessels occur normally, with a little experience pathologic alterations are readily recognized. Individual variations in the size of the cerebral arteries are probably dependent on the same

8. Turnbull, F.: Cerebral Angiography by Direct Injection of the Common Carotid Artery, Am. J. Roentgenol. **41**:166-172, 1939.

factors (age, sex, etc.) that determine the size of the arteries in general. The caliber of the blood vessels of the brain is influenced by vasomotor tone and by chemical and mechanical stimuli. It is probable that the injection of a 50 per cent solution of diodrast, which is markedly hypertonic, causes a change in the size of the cerebral arteries.

The configuration of the cerebral vessels in the lateral arteriogram has received considerable attention. The studies which my colleagues and I have made thus far have been limited to lateral projections. Variations in the internal carotid trunk may occur normally. One, two or even three loops may be present. The anterior cerebral artery was always visualized in our roentgenograms and was fairly uniform in position.

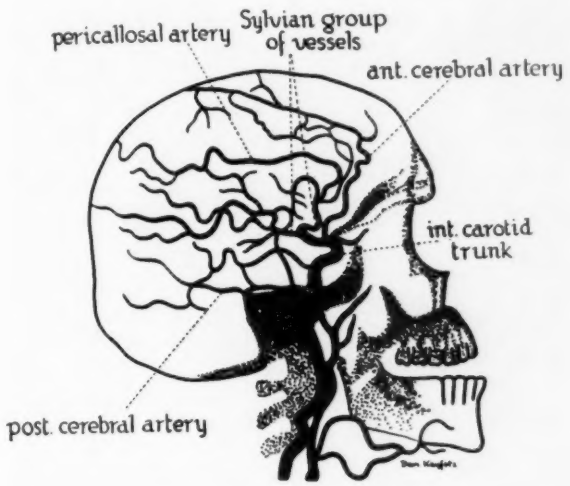


Fig. 2.—A normal arteriogram.

The sylvian group of vessels is a continuation of the middle cerebral artery. In the arteriogram, one, two or three main branches may be seen.

The posterior cerebral artery was not visualized in most of our arteriograms. This artery is normally a branch of the basilar and is not filled with the radiopaque substance when the common carotid artery is injected unless there is an unusually large posterior communicating artery on that side. Egas Moniz [1] stated that in about 15 per cent of normal persons the posterior cerebral artery is a branch of the internal carotid. This anomaly is generally unilateral. In cases of this type the posterior cerebral artery would be visualized.

APPLICATION OF CEREBRAL ARTERIOGRAPHY

My associates and I have carried out cerebral arteriographic examinations on 21 patients with a 35, 50 or 70 per cent solution of diodrast.

At present we recommend the use of a 50 per cent solution. The following cases illustrate the value of arteriography in neurologic diagnosis.

CASE 1.—A white woman aged 30 had had headaches for six and one-half years before an arteriogram was made. For the six or eight months preceding the study she complained of drowsiness, shooting pains in the left eye and double vision. She had been hospitalized on several previous occasions.

The patient was extremely thin. The left pupil was slightly larger than the right; the left palpebral fissure was narrower than the right, and sensation was diminished on the left side of the face. The results of laboratory studies, including a pneumoencephalographic examination, were normal. An arteriographic study was advised by the attending neurologist to rule out aneurysm.

Fig. 3 (case 1).—The arteriogram shows no abnormalities.

The left common carotid artery was exposed with local anesthesia and 12 cc. of a 50 per cent solution of diodrast injected. The external and internal carotid arteries appeared normal. The internal carotid trunk had three loops; the anterior cerebral artery and the sylvian group of vessels were normal. The posterior cerebral artery did not fill. There was no evidence of an intracranial aneurysm (fig. 3).

The patient had no reaction either during or after the injection of the 50 per cent solution of diodrast.

CASE 2.—A white woman aged 38 was admitted to the hospital for the first time in April 1938 because of failing vision, of five months' duration, and loss of smell, of eighteen months' duration. Examination disclosed bilateral anosmia and bitemporal hemianopia. The optic disk appeared normal. Visual acuity was 20/40 in the right eye and 20/60 in the left eye. The results of laboratory studies were normal; a roentgenogram of the skull, a pneumoencephalogram and exami-

nation of the spinal fluid revealed nothing significant. Fever therapy was instituted, without any change in the visual fields or in visual acuity.

The patient was readmitted to the hospital in December 1939 because of increased impairment of vision. The visual fields again showed bitemporal hemianopia. The nasal fields were contracted to 30 degrees on the right and 25 degrees on the left.

A right transfrontal craniotomy was done and the chiasmal region explored. The operator described his observations as follows: "The left optic nerve is thinner than the right, and a reddish brown mass is seen to the right and under the chiasm." Although needle exploration of the mass was not attempted, the operator concluded that the lesion was a "congenital aneurysm."

Fig. 4 (case 2).—Normal arteriogram. Note the position of the bone flap and the silver clip of a previous craniotomy.

The patient returned to the hospital for the third time in September 1940. The visual fields again showed bitemporal hemianopia, with marked constriction of the nasal fields. Because a diagnosis of "congenital aneurysm" had been made after an exploratory craniotomy, arteriographic study was recommended to verify or disprove this contention.

On Sept. 12, 1940, the right common carotid artery was exposed with local anesthesia and 20 cc. of a 50 per cent solution of diodrast injected. The patient had a jacksonian seizure immediately after the injection. The convulsion involved the left side of the face and the left upper extremity and lasted forty seconds. The arteriogram (fig. 4) showed a normal internal carotid trunk, with three loops. The anterior cerebral and the sylvian group of vessels were normal. The patient had no further reaction and no sequelae. In view of the normal arteriogram reexploration for the presumed neoplasm was advised, but the patient preferred

to defer this and was discharged from the hospital. Examination eight months later showed that, except for her visual disability, she was in good health.

CASE 3.—A white woman aged 45 was admitted to the hospital because of blindness. She had had headaches and dizzy spells for about ten years. For two months she had had "spots before the eyes" and failing vision, their appearance being followed shortly by severe headaches and vomiting. Two weeks before admission she became completely amaurotic. At this time her headaches ceased. Examination showed choked disks with secondary atrophy of the optic nerve, fixed pupils, loss of light perception, slight weakness in the left upper extremity and a Babinski sign on the left. A roentgenogram of the skull revealed small, powder-like deposits of calcium in the left occipital region. Because of the short history and the complete blindness, operative intervention did not seem justified unless the tumor was benign. An arteriogram was therefore advised. The left common carotid artery was exposed with local anesthesia and 20 cc. of

Fig. 5 (case 3).—Note calcification in the occipital region.

a 70 per cent solution of diodrast injected. The patient had a mild jacksonian seizure, involving the right side of the face and the right upper extremity and lasting about one minute. The arteriogram (fig. 5) showed absence of vessels in the region of the area of calcification. In addition, the sylvian group of vessels was displaced upward. A left occipital craniotomy was done and a large, hard, avascular tumor removed. On microscopic examination it proved to be an astrocytoma. The patient has been observed from time to time for eighteen months. She has not regained any vision, but is otherwise free from symptoms.

CASE 4.—A white man aged 54 was admitted to the hospital because of headache, dizziness and pain in the left leg. His illness began four months before with migratory joint pains, followed in a few weeks by severe frontal headaches and dizzy spells. Examination showed choked disks, a bilateral Babinski sign; inequality of the pupils, the left being larger than the right, and diffuse enlargement of the thyroid. The spinal fluid was under a pressure of 340 mm. of water and had a high protein content. While in the hospital the patient deteriorated

rapidly. Biopsy of the thyroid showed no evidence of malignancy. A ventriculogram was indicative of a right parietal mass. An arteriogram (fig. 6) showed marked increase in vascularity in the right parietal area and displacement of the sylvian group of vessels posteriorly. The appearance was that of malignant glioma. At operation a deep, infiltrating tumor was found.

CASE 5.—A white man aged 43 was admitted because of the sudden onset of right supraorbital pain, followed in thirty-six hours by inability to open the right eye. Examination showed complete paralysis of the right third nerve and slight increase in reflexes on the left side. The results of all laboratory studies, including electroencephalographic examination, were normal. The right common carotid artery was exposed with local anesthesia and 10 cc. of 50 per cent solution of diodrast injected. There was no reaction during or after the injection. The arteriogram (fig. 7) disclosed an aneurysm of the internal carotid trunk near the

Fig. 6 (case 4).—Note displacement posteriorly of the sylvian vessels and the increase in vascularity.

posterior communicating artery. The patient was discharged nine days later, after having been taught to compress the common carotid artery digitally. He continued digital compression at home. When seen in the clinic about six months later he was free from symptoms.

CASE 6.—A white man of 54 began to collide with objects on his right side about two months before his admission to the hospital. One month later left frontal headaches occurred, followed in a few days by irritability and difficulty in concentration.

Examination showed right homonymous hemianopia with macular sparing and early choked disks. An electroencephalogram was suggestive of a temporoparietal lesion, but the evidence was not conclusive. A pneumoencephalogram showed the lateral ventricles to be asymmetric and dilated. The interventricular

Fig. 7 (case 5).—The aneurysm is indicated by the arrow.

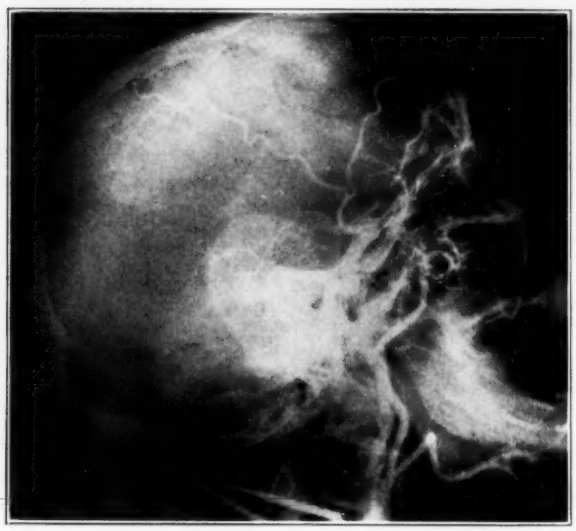


Fig. 8 (case 6).—The network of fine vessels in the occipital region is easily seen in the original arteriogram, but is only faintly visible in this reproduction.

septum was slightly deviated to the right. The third and fourth ventricles were normal. The changes indicated a mass on the left side, but more precise localization was not possible. Arteriographic study was therefore suggested to determine whether the lesion was in the temporal or in the occipital lobe. This examination was carried out with the injection of 10 cc. of a 50 per cent solution of diodrast into the left common carotid artery. The arteriogram (fig. 8) showed displacement of the sylvian group of vessels anteriorly and a fine network of small vessels in the occipital area. At operation an infiltrating glioma was observed near the under surface of the occipital lobe.

CASE 7.—(This case will be reported in greater detail at a later date.)

A white woman aged 42 was struck by an automobile. She was taken to a hospital, where she remained in a semistupor for seven days. When she became

Fig. 9 (case 7).—Traumatic arteriovenous aneurysm.

fully aware of her condition, she complained of a constant machinery-like noise in the right ear and of double vision. Her left eye became more prominent, and the eyelids were swollen.

She was admitted to the Mount Sinai Hospital about two months after her injury. Examination disclosed a loud systolic bruit, best heard in the left temporal region. The left eye was more prominent than the right and pulsated slightly. The left optic disk was slightly injected, and hearing was reduced on the left. Roentgenograms of the skull showed a linear fracture of the right temporal region, extending into the base.

Arteriographic study was carried out by exposing the left common carotid artery with the aid of local anesthesia and injecting 10 cc. of a 50 per cent solution of diodrast. The arteriogram (fig. 9) showed saccular aneurysm of the internal carotid artery in the cavernous sinus. The other structures visualized were venous channels filled with diodrast by reflux.

COMMENT

Cerebral arteriography provides an additional method for the investigation of lesions of the brain by visualizing alterations in size, shape and position of the cerebral blood vessels. Thus, information is obtained regarding both the location and the nature of the lesion. Aneurysms, arteriovenous fistulas, varices, vascular tumors, vascular malformations and other pathologic processes which involve the blood vessels are identified and localized with precision. Neoplasms and other space-consuming lesions are localized by the deformation which they produce in the cerebral arteries. This is especially helpful when pneumoencephalography fails to give the needed information. It is often possible to obtain some evidence regarding the nature of a neoplasm by the number, size and distribution of the vessels which supply it. This method has been employed in some European neurosurgical clinics to determine the operability of a cerebral tumor. Lorenz [9] attempted to differentiate glioblastomas, meningioma and sarcoma by means of arteriography. In cases of glioblastoma fine, small vessels, many of them forming a dense network, with lacunar widening in the region of the tumor, are found. In cases of meningioma the net-shaped and bundle-shaped small vessels that radiate into the tumor are easily recognized. In cases of intracranial sarcoma a combination of the features of the two other types is found. Cyst and abscess of the brain can be recognized by the absence of blood vessels in the region involved.[10] Intracranial aneurysms which simulate new growths are readily recognized by arteriography.

SUMMARY

Cerebral arteriography is an important adjunct to neurologic diagnosis. For the present it should be used only when accurate diagnosis is not attainable by other means.

Cerebral arteriography is indicated for the detection and localization of intracranial aneurysms, especially in recurring attacks of "spontaneous" subarachnoid hemorrhage. It is also indicated for the localization of intracranial arteriovenous fistulas, varices, vascular tumors and vascular malformations, for the differentiation of aneurysm and tumor and for the localization of neoplasms when the result of pneumoencephalographic examination is not conclusive.

When the technic outlined in this report has been followed and the contraindications have been observed, cerebral arteriographic examination with a 50 per cent solution of diodrast has proved a safe procedure.

Dr. Ira Cohen and Dr. Israel Wechsler permitted the use of material from their services.

9. Lorenz, R.: Differentialdiagnose der arteriographisch darstellbaren, intrakraniellen Geschwülste: Glioblastom, Meningeom, Sarkom, Zentralbl. f. Neurochir. **5**:30-61, 1940.

10. Egas Moniz: Cerebral Angiography, Lancet **2**:1144-1147, 1933.

News and Comment

SALMON COMMITTEE ON PSYCHIATRY AND MENTAL HYGIENE

Dr. R. D. Gillespie, who is now chief psychiatrist for the British Royal Air Force, is coming to this country at the request of the Salmon Committee on Psychiatry and Mental Hygiene of the New York Academy of Medicine. He will deliver the Thomas William Salmon Memorial Lectures in the New York Academy building November 17, 18 and 19, speaking on "Psychoneuroses from the Standpoint of War Experience."

The New York lectures will be followed by addresses before the Chicago Neurological Society, the Chicago Institute of Medicine and the Illinois Psychiatric Society in Chicago. Dates for these lectures, as well as for lectures in Toronto, Canada, and San Francisco, will be announced later.

Dr. Gillespie's observations made under actual war conditions are expected to be of inestimable value to American psychiatrists in formulating plans for maintaining civilian morale in wartime. His lectures will also give his hearers new information concerning the pressing psychiatric problem of today—the psychoneuroses.

APPOINTMENT OF DR. BOWMAN TO LANGLEY PORTER CLINIC

Dr. Karl Murdock Bowman has been selected by the faculty of the University of California Medical School and the regents of the University and by the Department of Institutions for appointment to take charge of the Langley Porter Clinic in San Francisco.

Dr. Bowman, at present, is director of the Division of Psychiatry, New York City Hospitals, and professor of psychiatry at New York University. He was born in Topeka, Kan., in 1888 and received his medical degree at the University of California in 1913.

Dr. Bowman is expected to report for duty at the Langley Porter Clinic on or about Nov. 1, 1941.

AMERICAN PSYCHIATRIC ASSOCIATION

The Military Mobilization Committee has brought out a further compilation for the use of the members of the association who are being called on to discuss or deal with problems of civilian mental health during the present period of stress. The subject of the compilation is "Social Institutions During Periods of Stress." Copies may be obtained on request from Dr. D. Ewen Cameron, Albany Hospital, Albany, N. Y.

Abstracts from Current Literature

Anatomy and Embryology

INNERVATION OF THE HYPOPHYSIS OF THE RABBIT AND RAT. C. McC. BROOKS and I. GERSH, Endocrinology **28**:1 (Jan.) 1941.

Brooks and Gersh describe histologic studies of the hypophysis of young rabbits and rats, thus enlarging the anatomic basis for the physiologic evidence of direct nerve control of certain hypophysial functions. The specimens were prepared by the pyridine-silver method, and serial sections were made. Observations were made on animals after superior cervical ganglionectomy and section of the hypophysial stalk and on normal controls. It was found that nerve fibers of the neurohypophysis originate in the hypothalamus, some of these continuing into the pars intermedia and the anterior lobe. In the rabbit, and possibly also in the rat, these fibers in the adenohypophysis are supplemented by a smaller number arising from the carotid plexus. In the rat nerve fibers were seen to terminate in what has been interpreted as pericellular nerve nets around gland cells of the infundibular process and the anterior lobe.

PALMER, Philadelphia.

EXPERIMENTAL CHANGES IN END-FEET OF HELD-AUERBACH IN THE SPINAL CORD OF THE CAT. RUTH I. BARNARD, J. Comp. Neurol. **73**:235 (Oct.) 1940.

Barnard's experiments on the changes in the end feet of Held and Auerbach in the spinal cord of the cat were designed to show the nature and lability of the end foot type of synapse in the spinal cord, its reaction to injury of the nerve cell and its relation and connection with both the cell of origin and the cell of termination. The end feet were demonstrated by Cajal's impregnation method or by Mallory's connective tissue stain after perfusion with Regaud's formaldehyde-potassium bichromate fixative. The normal appearance of end feet in Cajal material was that of round, elliptic or elongated masses or of reticulated or granular structures. The total number seen on a cell varied from a few to a hundred or more. In material stained with Mallory's stain the end feet appeared as round, solid, somewhat granular bodies. Barnard destroyed by electrocautery the entire cruciate gyrus unilaterally in 5 cats, which were killed from three to seven days later. Sections of the cervical and lumbar segments of the spinal cords were prepared to show end feet. Study was made of end feet on the anterior horn cells and on the cells of the intermediate column. The end feet persisted in these animals and appeared to be within the limits of normal variation. Next, a series of cats was subjected to hemisection of the midthoracic portion of the cord plus section of two to four dorsal roots at and below the level of section. The animals were killed from two to thirty-six days later. None of the cats showed any difference in end feet of cells on the two sides of the spinal cord below the level of the lesion. In a series of cats in which the ventral root was cut, the end feet of the chromatolyzed anterior horn cells fragmented and disappeared in increasing numbers. Barnard does not believe that the Cajal method is suitable for following fiber tracts to their termination in the spinal cord.

FRASER, Philadelphia.

EXPERIMENTAL STUDIES ON THE INTRINSIC FIBERS OF THE CEREBELLUM: II. THE CORTICO-NUCLEAR PROJECTION. JAN JANSEN and ALF BRODAL, J. Comp. Neurol. **73**:267 (Oct.) 1940.

Jansen and Brodal produced lesions in different divisions of the cerebellar cortex of 39 rabbits and 32 cats by a Graefe knife or by thermocautery. The

animals were kept alive for from twelve to twenty days, after which the brains were prepared by the Marchi technic. In the cat, lesions in the vermis produced degeneration of fibers going to the medial cerebellar nuclei and to the nucleus of Deiters. Lesions in the lateral parts of the anterior lobe produced degeneration of fibers going to the nucleus interpositus. Lesions in the ensiform lobule produced degeneration of fibers to the dorsomedial parts of the lateral cerebellar nucleus. Lesions in the paraflocculus produced degeneration of fibers to the lateral cerebellar nucleus. Lesions in the paramedian lobule produced degeneration of fibers going to the caudomedial parts of the fused lateral and intermediate cerebellar nuclei. The rabbit material was incomplete, but it substantiated the observations on the cat. Jansen and Brodal conclude that the extreme lateral part of the nucleus lateralis (dentatus) is not the youngest part of this nucleus in cats and rabbits, as it is in man.

ADDISON, Philadelphia.

FURTHER NOTES ON THE VERTEBRATE SYNAPSE. DAVID BODIAN, J. Comp. Neurol. **73**:323 (Oct.) 1940.

Bodian describes the axon endings in goldfish after perfusion with Zenker-formaldehyde fixative followed by the Mallory-azan stain. The size of the endings varied from 0.5 to 7 microns. The smallest end feet were usually the terminals of the finest fibers. These were usually unmyelinated, but the range in size was only partly dependent on the size of the fiber of which it was the terminus. Whenever synapsing fibers were myelinated, whether these fibers were large or small, the myelin sheath terminated abruptly a short distance proximal to the contact surface. All endings appeared to have an accumulation of mitochondria near the terminal membrane, which was adherent to the cell of termination.

ADDISON, Philadelphia.

THE DIENCEPHALIC CELL MASSES OF THE TELEOST, CORYDORA PALIATUS. RUTH N. MILLER, J. Comp. Neurol. **73**:345 (Dec.) 1940.

For the study of the diencephalon of the silurid corydora paliatus, cell and fiber preparations were available. Comparison was made with brains of a selachian and of 2 amphibians prepared in a similar manner. Wax plate and graphic reconstructions were made. The rostral boundary of the diencephalon is the anterior commissure, the sulcus terminalis telencephali and the attachment of the velum transversum. The caudal boundary is at the posterior commissure. The four longitudinal cell zones—the epithalamus, the dorsal and the ventral thalamus and the hypothalamus—were identified. Miller attempts to analyze the arrangement of the cell masses in each of these zones and their relation to the several sulci. The dorsal thalamus is well developed, while the ventral thalamus is relatively small. The posterior hypothalamus is more complex than that found in selachians, dipnoi and amphibians. In general the pattern of the diencephalon found in Corydora paliatus is directly comparable to that found in these three groups, but is more differentiated.

FRASER, Philadelphia.

THE FUNCTIONAL RESULTS OF MUSCLE TRANSPOSITION IN THE HIND LIMB OF THE RAT. ROGER W. SPERRY, J. Comp. Neurol. **73**:379 (Dec.) 1940.

Sperry undertook a study of the functional results of muscle transposition in the hindlimb of the rat because of the scarcity and inconsistent interpretation of data on functional results of nerve and muscle crossing in mammals. He interchanged the tendons of the two main dorsiflexors of the foot (the tibialis anterior and the extensor digitorum longus) with the tendon of a muscle producing plantar flexion (gastrocnemius lateralis). All other muscles of the shank were removed. Of the animals operated on, 9 showed complete free movement of the joint approximately the normal 170 degrees and were observed and tested for periods varying from five to fifteen and a half months after operation. There was no sign of any functional adjustment whatever in the action of the transposed muscles.

In another rat the nerves were crossed instead of the muscles; the operation otherwise was similar. The result was the typical reversal of foot movement characteristic of muscle transplantation. In 2 other animals both nerves and muscles were transplanted. The nerves were crossed first, and after allowing time for regeneration, the muscles were transposed in a second operation. On recovery these rats showed good movement of the foot in normal phase. The double negative result gave a positive effect.

In control animals, in which the plantar and dorsiflexor muscles were transplanted and the other muscles of the shank left intact, the intact muscles were strong enough to overpower the action of the transposed muscles, so that the movements of the foot were closer to normal than to reversed action. Sperry attributes the inability of the rat to modify the reversed foot movement, as contrasted with the experience of human beings, to the primitive condition of the nervous system of the rat.

ADDISON, Philadelphia.

A STRUCTURAL ANALYSIS OF THE LATERAL GENICULATE NUCLEUS OF THE CAT. JAMES L. O'LEARY, J. Comp. Neurol. **73**:405 (Dec.) 1940.

O'Leary studied the dorsal nucleus of the lateral geniculate body in an attempt to demonstrate a neural pattern which would suffice for establishing intranuclear circuits of electrical activity. The chief material studied consisted of Golgi preparations of 130 blocks of brain tissue from kittens between 8 and 18 days old. Nissl series of brains of adult cats were used for glass plate reconstructions and for a model in plastocene of the lateral geniculate body. O'Leary confirmed the observations of earlier investigators on the cellular structure. There are three cellular laminas in the dorsal nucleus. The cells are of two kinds, the principal and the short axon cells. The principal cells are those the axons of which enter the optic radiation. The short axon cells have axons which branch repeatedly and arborize terminally near the cell body. In the optic tract as it approaches the geniculate bodies are large and small fibers. The large ones bifurcate into thick and thin branches. The thick branches end in one of the cellular laminas, without collaterals. The thin branches become lost, and it is supposed that they may either end within the geniculate body or pass toward the midbrain. O'Leary finds that the small optic nerve fibers send collaterals to the ventral nucleus and then probably continue toward the midbrain. The ventral nucleus of the lateral geniculate body is small and the cells are spindle shaped.

Electrophysiologic experiments demonstrate fast conduction through the dorsal nucleus, with no sequelae of sustained activity. O'Leary relates this to the lack of collaterals on the axons of the principal cells. The numerous short axon cells, each confined for the most part to one cellular lamina, are probably part of a synchronizing mechanism.

FRASER, Philadelphia.

THE DEVELOPMENT OF THE OLFACTORY AND THE ACCESSORY OLFACTORY FORMATIONS IN HUMAN EMBRYOS AND FETUSES. TRYPHENA HUMPHREY, J. Comp. Neurol. **73**:431 (Dec.) 1940.

Of the 13 human fetuses used in this study, 11 had been tested for their reactivity to external stimuli and photographed in moving pictures. The series ranged from 14 to 145 mm. in length. Up to the 37 mm. stage the entire fetus was sectioned. From the 49 mm. stage onward the brain was removed and sectioned separately. Some series were stained for cells and others by Bodian's silver technic. Recognition of the primordia of both olfactory and accessory olfactory formations was possible in the 26 mm. fetuses, which had a menstrual age of 8 to 8.5 weeks. At this time each formation showed three layers, which apparently corresponded to the ependymal, mantle and marginal layers characteristic of the developing neural tube. From these layers there developed a laminated cortex of five layers

in both formations. In the 145 mm. fetus, menstrual age 18.5 weeks, the olfactory formation showed the lamination pattern as well differentiated as in the adult. In the same fetus the accessory olfactory formation was still demonstrable. Before this stage, however, beginning at the 49 mm. stage, menstrual age 11 weeks, regressive changes had appeared on one or both sides. The accessory olfactory formation is absent in the adult human brain. The development and regression of the accessory olfactory formation parallel the history of the vomeronasal organ, or organ of Jacobson, in man.

ADDISON, Philadelphia.

THE DIFFERENTIATION OF THE MOTOR CELL COLUMNS IN THE CERVICAL CORD OF ALBINO RAT FETUSES. A. W. ANGULO Y GONZÁLEZ, J. Comp. Neurol. **73**:469 (Dec.) 1940.

Fetuses of albino rats taken at eight hour intervals from fourteen to twenty days after insemination were used for these observations on the differentiation of the motor cell columns in the cervical portion of the cord. Part of the material was tested for reactions to various stimuli. Sections of entire fetuses were made at 5 to 10 microns. The series were stained to show cells or prepared by a Cajal silver technic. The division between the medulla and the cervical portion of the spinal cord was taken as the halfway line between the most caudal rootlets of the hypoglossal and the most rostral rootlets of the first cervical nerve. The author finds that the early differentiation of the motor cell columns progresses gradually from the cephalic to the caudal end. At the fourteenth fetal day there is a single undifferentiated cell mass. Nissl substance is present only at the poles of the nuclei. Fetuses of this stage do not react to experimental stimuli. During the succeeding days there emerge from the single cell mass the twelve cell columns described for the rat at birth. Nissl substance appears at the periphery of the cell and throughout the cytosome. At the seventeenth day segregation of the cells into groups is almost complete, yet the behavioral activity of the animal continues to be that of total mass activity up to the early part of the nineteenth day. Unit reflex activity begins in the latter part of the nineteenth day. Thus both pattern of growth and pattern of behavior proceed from the total to the part.

FRASER, Philadelphia.

REACTIONS OF DORSAL ROOT GANGLION CELLS TO SECTION OF PERIPHERAL AND CENTRAL PROCESSES. WILLIAM KENDRICK HARE and JOSEPH C. HINSEY, J. Comp. Neurol. **73**:489 (Dec.) 1940.

Experiments were performed on 19 cats in order to compare the effect of cutting the afferent process of a nerve cell with the effect of cutting the efferent process. The majority of the experiments consisted in cutting one or more dorsal roots between the ganglion and the spinal cord in the lumbosacral region of one side and the sciatic nerve of the other. The spinal ganglia were examined histologically at comparatively short periods after operation, ranging from six to thirty-five days. Section of the central processes produced no effect on the ganglion cells of the dorsal roots involved, but on the side on which the sciatic nerve had been cut there were chromatolytic changes in some of the cells of the spinal ganglia. These differences in reaction remain to be explained.

ADDISON, Philadelphia.

Physiology and Biochemistry

THE DISTRIBUTION OF SULFANILAMIDE BETWEEN BLOOD AND CEREBROSPINAL FLUID WITH SPECIAL REFERENCE TO INTRASPINAL TREATMENT. S. KATZENELBOGEN, B. A. CRUVANT and C. SILVERBERG, Am. J. M. Sc. **201**:830 (May) 1941.

Katzenelbogen, Cruvant and Silverberg carried out studies on 31 normal patients in whom the cerebrospinal fluid was normal. For the determination of

sulfanilamide in the blood and cerebrospinal fluid the method of Bratton and Marshall was used. Sixteen schizophrenic patients with no physical disease received by mouth therapeutic doses of sulfanilamide, namely, 25 grains (1.625 Gm.) every six hours, plus 15 grains (0.975 Gm.) of sodium bicarbonate, or a total of 100 grains (6.5 Gm.) in twenty-four hours. The medication was discontinued at the end of the third day. The permeability quotients varied from 1.06 to 1.68 at the end of the first day of medication, from 1.17 to 1.44 at the end of the second day and from 1.19 to 1.36 at the end of the third day. For 10 patients (5 psychotic patients with general arteriosclerosis and 5 psychotic patients with organic disease) who received single doses (2 or 5 Gm. of sulfanilamide) the permeability quotients ranged between 1.33 and 2.92 four hours after administration of the drug and between 0.71 and 1.23 twenty-eight hours after the drug was given. The authors concluded that oral administration of sulfanilamide assures the penetration of the drug into the cerebrospinal fluid in concentrations sufficiently high to render unnecessary intraspinal administration.

MICHAELS, Boston.

THE B VITAMINS AND FAT METABOLISM: IV. THE SYNTHESIS OF FAT FROM PROTEIN. E. W. McHENRY and GERTRUDE GAVIN, J. Biol. Chem. **138**:471, 1941.

While the administration of thiamine hydrochloride alone will cause the synthesis of fat from carbohydrate, it will not produce a similar result with protein. In the case of the latter pyridoxine is essential. This vitamin, in combination with thiamine, prevents a reduction in body fat of rats maintained on a protein diet. The synthesis of fat from protein is clearly evident when pyridoxine, thiamine, riboflavin and pantothenic acid are supplied. Various combinations of the isolated members of the vitamin B complex do not cause the synthesis of fat from protein unless pyridoxine is present. It is suggested that pyridoxine is essential for the metabolism of protein.

PAGE, Indianapolis.

"COUPLING" OF PHOSPHORYLATION WITH OXIDATION OF PYRUVIC ACID IN BRAIN. S. OCHOA, J. Biol. Chem. **138**:751, 1941.

The dialyzable components of the pyruvic acid oxidation system in brain consists of at least (1) cocarboxylase, (2) a C_4 dicarboxylic acid, (3) magnesium and manganese ions and (4) inorganic phosphate and "adenine nucleotide" (adenylic acid or adenosine triphosphate). The fact that the last-named substance is required suggests that a cycle of phosphorylation is involved in the enzymatic oxidation of pyruvate. Ochoa has studied the relation between phosphorylation and oxidation in brain. He finds that no more than half of the esterification of inorganic phosphate with either hexose monophosphate or dextrose, occurring in brain dispersions when pyruvate is oxidized (with fumarate as catalyst), can be related to oxidation of a dicarboxylic acid; the rest is connected with oxidation of pyruvate itself. Evidence has also been obtained to support the view that oxidation of pyruvate is connected with phosphorylation of adenylic acid to adenosine polyphosphate, which transfers its labile phosphate groups to either hexose monophosphate or dextrose with formation of hexose diphosphate. The mechanism of phosphorylation in brain dispersions can be pictured as follows: With catalytic amounts of adenylic acid, and in the absence of further phosphate acceptors, the adenosine triphosphate, formed by reaction of adenylic acid with the hypothetic phosphorylated oxidation product of pyruvic acid, is rapidly dephosphorylated by the adenosine triphosphatase, and adenylic acid is regenerated for further reaction; the concentration of inorganic phosphate remains unchanged. It is due to the presence of adenosine triphosphatase that oxygen consumption can take place independently of the phosphorylation of a phosphate acceptor, but, in the absence of added adenylic acid, the concentration of preformed "adenine nucleotide" in the dialyzed dispersions is too low to keep this mechanism working at a sufficiently high rate, and the rate of oxygen uptake falls below normal. In

the presence of both adenylic acid (in catalytic amounts) and phosphate acceptors for the labile phosphorus groups of adenosine triphosphate, such as hexose monophosphate or dextrose, a greater or lesser proportion of the adenosine triphosphate escapes the action of adenosine triphosphatase by transferring phosphate to the acceptor with formation of hexose diphosphate; an equivalent amount of inorganic phosphate disappears. The fact that phosphorylation of adenylic acid is an obligate step in dehydrogenation of both triose phosphate and pyruvate makes it the main mechanism by which the energy of respiration is made available to the tissues. The results on which this is based are that dialyzed dispersions from pigeon brain in the presence of sodium fluoride and all the components of the pyruvate oxidation system show a limited capacity to phosphorylate adenylic acid or creatine. With catalytic amounts of adenylic acid, added hexose monophosphate or dextrose is phosphorylated to hexose diphosphate with uptake of an equivalent amount of inorganic phosphate. The presence of adenylic acid is indispensable. Under the conditions of these experiments phosphorylation is connected with the oxidation of pyruvate catalyzed by C_4 dicarboxylic acids, since (*a*) without pyruvate-fumarate there is neither oxygen uptake nor phosphorylation; (*b*) in brain dispersions from vitamin B_1-deficient pigeons esterification is increased by addition of cocarboxylase to the same extent as removal of pyruvate and oxygen consumption and (*c*) arsenite blocks the esterification by inhibiting the oxidation of pyruvate. Under certain conditions the ratio of atoms of phosphorus esterified to molecules of oxygen taken up is constant. This ratio has a maximum value of 4 at the beginning but decreases with time, owing to inhibition of esterification by the accumulating phosphorylation product. With catalytic amounts of adenylic acid, brain dispersions catalyze phosphorylation to hexose diphosphate, of either hexose monophosphate or dextrose, by anaerobic transfer of phosphate from phosphopyruvic or phosphoglyceric acid, showing that the labile phosphate groups of adenosine triphosphate are transferred to either of the two P acceptors.

Thus the necessity of adenylic acid for aerobic phosphorylation can be best interpreted by assuming that oxidation of pyruvate is linked with phosphorylation of adenylic acid to adenosine polyphosphate, which then transfers its labile phosphate to hexose monophosphate or dextrose. Relative to the oxygen consumption phosphorylation is much decreased in the absence of fluoride. The effect of fluoride is believed to be due to depression of the activity of adenosine triphosphatase. Both oxygen uptake and phosphorylation are relatively resistant to iodoacetic acid and are depressed by it to the same extent. Oxidation of succinate by brain dispersions is also accompanied by phosphorylation of hexose monophosphate or dextrose. When arsenite is added, to prevent oxidation of any pyruvate which may be formed, the ratio of atoms of phosphorus esterified to molecules of oxygen taken up is half or less of that obtained (without arsenite) with pyruvate-fumarate. Hence catalytic action of C_4 dicarboxylic acids by itself can account for no more than half of the phosphorylation connected with pyruvate oxidation.

PAGE, Indianapolis.

FURTHER OBSERVATIONS ON THE WATER DRIVE IN TRITURUS VIRIDESCENS: II. INDUCTION OF THE WATER DRIVE WITH THE LACTOGENIC HORMONE. C. S. CHADWICK, J. Exper. Zool. **86**:175 (March) 1941.

The land phase of the newt Triturus viridescens migrates to water in the autumn of the year in which it reaches maturity. The stimulus which causes this migration appears to be powerful. Previous work had shown that animals in the land phase could be driven to water out of season by intramuscular implants of the pituitary of the adult Triturus. In the present study, red efts of Triturus were caused to assume a water habitat by intraperitoneal implants of the anterior pituitary from a toad, a water snake or a chicken. The water drive factor was also found to exist in the pituitaries of red efts of various sizes and ages. Injections of crystalline prolactin, isolated from the mammalian pituitary gland,

also caused the red efts of Triturus to assume a water habitat and to undergo the changes necessary for complete adaptation to water. It was effective in the absence of thyroid and gonads, in either sex and in efts of all sizes.

WYMAN, Boston.

OBSERVATIONS ON CORTICAL SOMATIC SENSORY MECHANISMS OF CAT AND MONKEY. W. H. MARSHALL, CLINTON N. WOOLSEY and PHILIP BARD, J. Neurophysiol. **4**:1 (Jan.) 1941.

The application of a brief tactile stimulus of low intensity to a very small cutaneous area evokes discrete surface positive potential waves in specific places on the contralateral cortex of the cat or the monkey. These potentials constitute the primary cortical response to sensory stimulation.

In the cat a weak tactile stimulus applied to hairs on the dorsal surface of the forepaw (the only peripheral area given detailed examination) evokes separate maximal primary responses at three regions on the contralateral cortex. In the monkey the application of such a stimulus to any part of the body always evokes primary responses at two or more regions within the cortical area of representation of that part. The response having the shorter latency occurs in area 3 (Brodmann); the other, with slightly greater latency, is usually found in area 2. A third region of maximal primary response is often found in, or very near, area 1.

Each region or spot of maximal primary response is surrounded by a fringe or margin of submaximal responses. The overlap of the submaximal margins for peripheral regions which are adjacent or which have adjacent cortical representations is reciprocal and definite. Demonstrable interaction is usually found within the overlap.

Sodium pentobarbital and certain other anesthetics greatly reduce the spontaneous activity of the cortex but do not appreciably affect any characteristics of the primary response except the recovery time, which is greatly prolonged.

Moderate ether anesthesia does not reduce the spontaneous activity of the cortex, and it does not appreciably affect the threshold, latency or size of the primary response. With ether, even extremely deep ether anesthesia, the recovery time is shorter than with anesthesia induced by pentobarbital sodium. With light and moderate ether anesthesia the absolutely unresponsive time is very short.

The primary response is present in the absence of anesthesia. As compared with the responses evocable in the anesthetized preparation, those of the unanesthetized animal are characterized by a shorter recovery time of the primary response, greater complexity of various secondary reactions and the occurrence of long-lasting facilitation effects.

ALPERS, Philadelphia.

PUPILLODILATOR REACTIONS TO SCIATIC AND DIENCEPHALIC STIMULATION. E. A. WEINSTEN and M. B. BENDER, J. Neurophysiol. **4**:44 (Jan.) 1941.

Comparative studies of pupillary dilatation obtained on stimulation of the sciatic nerve and the diencephalon were made in the cat and monkey.

The reflex pupillary dilatation obtained with sciatic stimulation in the cat was not abolished by section of the cervical sympathetic trunk or the trigeminus nerve or by lesions of the hypothalamus, but the reaction was eliminated by section of the oculomotor nerve.

In contrast, this reflex pupillary dilatation in the monkey was abolished or greatly reduced by cutting of the cervical sympathetic trunk, but it failed to disappear after section of the third cranial nerve.

Similarly, the pupillary dilatation obtained by stimulation of the thalamus or the dorsal portion of the hypothalamus in the cat was little reduced by section of the cervical sympathetic trunk, and it could not be obtained by sectioning the third cranial nerve.

Stimulation of the hypothalamus in the monkey resulted in bilateral pupillary dilatation, which was abolished, or greatly diminished, by section of the cervical sympathetic trunk, but it was not abolished by destruction of the oculomotor nerve.

In each species pupillary dilatation is accomplished by both the parasympathetic inhibitory and the sympathetic excitatory mechanism. In the cat inhibition of the parasympathetic mechanism is predominant, while in the monkey excitation of the sympathetic mechanism is of greater importance. ALPERS, Philadelphia.

Neuropathology

INTRACEREBRAL VASCULAR CALCIFICATION. W. VOLLAND, Arch. f. Psychiat. **111**:5 (Jan.) 1940.

Volland distinguishes two types of deposits of calcium in the brain: (1) calcification of necrotic tissues and (2) nonarteriosclerotic vascular calcification. The second type may be either symptomatic or idiopathic. The idiopathic form apparently affects primarily the extrapyramidal centers and is considered as forming a well differentiated disease entity. The disease process is chronic and is characterized clinically by spastic paresis, disturbances in coordination and mental deterioration. Anatomically, calcifications occur in the vessels of the thalamus, the striate body, the pallidum and the dentate nucleus. Histologically, one finds primarily calcifications of the capillaries. These merge into the development of compact, cufflike structures and finally produce obliteration of the lumen and a so-called brain stone. The author stresses particularly the fact that the disturbances seem to show special predilection for the extrapyramidal system and show little or no tendency to invade other structures. MALAMUD, Worcester, Mass.

PATHOANATOMIC CHANGES IN CASES OF DEATH FOLLOWING INSULIN AND METRAZOL SHOCK TREATMENT. J. JANSEN and E. WAALER, Arch. f. Psychiat. **111**:62 (Jan.) 1940.

Jansen and Waaler report on histologic studies in 7 cases in which the patient died after shock therapy—in 6 after insulin and in 1 after metrazol treatment. Three of the cases (including that in which metrazol was implicated) must be regarded as instances of death due to cerebral causes. In the other 4 cases the cause of death was not primarily related to the treatment.

In the first 3 cases the changes consisted mainly of ischemic areas in the cortex, some of them with pseudolaminar distribution. In 1 case the disturbances also occurred in the striate body, accompanied by diffuse glial proliferation and some vascular changes. In the other 2 cases there were hemorrhagic infarcts. In the case in which metrazol was employed, glial rosettes were observed in the white matter; there were also areas of isolated neuronophagia. In the 4 cases in which death was considered incidental to the treatment there were a few isolated subarachnoid and perivascular hemorrhages. Changes were found also in the pancreas and in the adrenal glands.

The author concludes that repeated administration of insulin need not of itself cause lasting changes in the central nervous system or in other organs. In the cases reported the changes occurred in the early stages of the treatment, after relatively small doses of insulin. He concludes that individual characteristics of the patient rather than the insulin itself should be considered as responsible for the damage. MALAMUD, Worcester, Mass.

AN OLD GUNSHOT WOUND WITH MESENCHYMAL SCARRING OF THE COURSE OF THE BULLET AND LATE MENINGITIS. WALTER MÜLLER, Arch. f. Psychiat. **111**:209 (March) 1940.

Müller reports a case of a 34 year old man who, four years before his death, made a suicidal attempt by shooting himself through the right temple, the bullet

coming out through the left temple. Following this attempt there was fairly rapid convalescence, with little apparent mental change and no neurologic signs. Shortly before death, and without any exciting stimuli, meningitis developed, which terminated fatally. Postmortem examination showed rapidly progressing meningococcic meningitis, with an unusually intensive mesenchymal scarring of the intracerebral course of the bullet. The case supports the previously advanced theory of Esser that scarring in gunshot wounds of the deeper layers of the brain occurs only in the presence of subsequent infection, no matter how late this may occur.

MALAMUD, Worcester, Mass.

CHANGES IN THE BRAINS OF ANIMALS FOLLOWING METRAZOL AND CAMPHOR CONVULSIONS. W. ROTTER and P. KRUG, Arch. f. Psychiat. **111**:380 (May) 1940.

Rotter and Krug produce typical convulsions with metrazol and camphor in guinea pigs and rabbits. In several groups of guinea pigs, it was observed that the animals which died in the first convulsion showed no histologic changes. Animals which survived at least one convulsion showed isolated irreversible changes in the ganglion cells, of the type known as Nissl's "severe ganglion cell disease." In cases of status epilepticus severe and extensive cell changes were produced; these were dependent on the duration of the convulsions. In some of the animals which were killed some time after a convulsion, various stages of degeneration, probably referable to the repeated convulsions, were observed. In 1 animal no changes were seen, although it was killed during particularly severe status epilepticus. In two groups of rabbits treated with smaller doses the convulsions produced no changes, suggesting that the degree of pathologic injury is definitely related to the quantity of the drug used.

MALAMUD, Worcester, Mass.

CHANGES IN THE NERVOUS SYSTEM IN A CASE OF PUERPERAL ECLAMPSIA. S. KÖRNYEY, Arch. f. Psychiat. **112**:243 (Nov.) 1940.

Környey reports a case of puerperal eclampsia in which the clinical manifestations presented the picture of a severe decerebration symptom complex accompanied by signs of focal irritation and destruction of tissue. The most important pathologic changes consisted in extensive destruction of cells in various parts of the cortex and geniculate bodies, accompanied by pronounced glial reactions. There were also thick glial networks in the molecular layer of the cerebellum. A benzidine section showed alternating anemic and hyperemic areas in the cortex which bore no consistent relation to the lesions of the ganglion cells. Környey is of the opinion that this lack of relation indicates that the vascular disturbances thus demonstrated are a manifestation of conditions directly preceding death. He concludes that both the clinical picture and the histologic changes support the contention that the disease is one determined primarily by disturbances of circulation.

MALAMUD, Worcester, Mass.

NEUROPATHOLOGIC SYNDROMES AFTER ELECTRICAL INJURY. FRIEDRICH SCHEIFFARTH, Deutsche Ztschr. f. Nervenh. **151**:153, 1940.

Though several reports have dealt with the causal connection between disease of the nervous system and electrical accident, the actual mechanism of the pathologic process is not yet clear. Statistically, neuropathologic changes most frequently affect the peripheral nerves, the anterior horns of the spinal cord, the cervical and dorsal portions of the cord and the peripheral or central parts of the vegetative nervous system. This coincides with the most frequent course of the electric current through the upper extremities, thorax and cervical portion of the cord. Cerebral syndromes may occur regardless of whether or not the brain was within the course of the electric current. Alternating current is more likely to cause

damage than direct current. High voltage currents are apparently most dangerous. Individual susceptibility is of greatest importance. The pathologic process usually results in the establishment of a systemic disease of the nervous system which can hardly be differentiated from similar syndromes of other origin. The author describes 4 cases, in 3 of which "vegetative paresis" had developed after electrical injuries. This consisted of weakness of an extremity with cyanosis, hyperhidrosis, changes in cutaneous temperature, pain and, in 1 case after three weeks, gangrene of the hand. In the fourth case, that of a 45 year old man, paralysis agitans developed "shortly after the accident." The author is aware that no proof exists for the assumption of a causal connection between the electrical accident and parkinsonism in the last case.

ADLER, Boston.

Psychiatry and Psychopathology

CHANGE OF PERSONALITY AS A SEQUEL OF ACUTE CARBON MONOXIDE POISONING. J. M. NIELSEN and SAMUEL D. INGHAM, Bull. Los Angeles Neurol. Soc. **5**:185 (Dec.) 1940.

The mechanism of the neurologic changes following asphyxia with carbon monoxide is not understood, and especially unclear are those cases in which apparent recovery is followed by relapse and incapacity or death. Nielsen and Ingham report 4 cases in which the patients all "recovered" from acute asphyxia due to carbon monoxide, only to exhibit marked changes of personality. The outstanding mental characteristics after poisoning were apathy, lack of initiative and indifference to duties, responsibility, pleasures and even sexual urge. Amnesia was a feature in 2 cases, and parkinsonism was suggested in the usual presence of muscular rigidities, tremor, masked facies or loss of associated movements. Other organic neurologic signs included weakly positive pathologic reflexes and, in 1 case, homonymous hemianopia. In this case the patient died a month after asphyxia, and autopsy exhibited, in addition to bilateral necrosis of the globus pallidus, disseminated cortical and subcortical areas of destruction. Nielsen and Ingham consider the mental changes described as classic for carbon monoxide asphyxia.

MACKAY, Chicago.

PSYCHOSES ASSOCIATED WITH ESSENTIAL HYPERTENSION. M. D. REIMER, Psychiatric Quart. **15**:284 (April) 1941.

Reimer studied 5 schizophrenic patients with essential hypertension. No characteristic symptoms were found, though exhibitionism, abnormal sex life and perfectionistic attitudes with attendant guilt feelings were common. In 3 patients the hypertension tended to subside after some months of excitement and overt hostility. During the period of relative hypotension these patients showed defensive mechanisms in personality changes, which were interpreted as a defense against anxiety, to which the period of excitement and hostility was itself a reaction. The reduction in blood pressure appeared to be associated with the partial abreaction of hostility. In 2 patients the hypertension persisted. These persons showed no periods of excitement which could drain off the hostility and the underlying anxiety. All the patients were said to have suffered from deprivation of parental love and were strongly narcissistic, consequently becoming anxious readily at any sign of deprivation. The delusional systems were unimaginative, and the paucity of ideation was thought, perhaps, to limit outlets for expression and thus force the patients to "seek somatic expression through the cardio-vascular system."

SIMON, Worcester, Mass.

A PSYCHODYNAMIC STUDY OF RECOVERY OF TWO SCHIZOPHRENIA CASES. THOMAS M. FRENCH and JACOB KASANIN, Psychoanalyt. Quart. **10**:1, 1941.

French and Kasanin, attempt to explain why certain psychotic patients recover with no treatment except good physical care and the sympathetic interest of the

physician. They report in detail the cases of 2 schizophrenic persons who recovered under this regimen. In both, it was found that the psychotic episode represented a step in the process of giving up the childhood dependency on the parents and learning how to find a solution for their sexual needs in a heterosexual life.

In this process of growing up, the psychotic attack was the expression of a feeling of frustration which resulted from the abandonment of old methods of obtaining sexual gratification before new methods had been learned. Reactions expressing such frustration are common in puberty, since it is not to be expected that a new method of adjustment can be learned at once. During the process of learning new methods of adaptation, two main trends are found: (1) a reaction to the feeling of frustration which results from the abandoning of the old methods before new ones are found, and (2) a constructive impulse to solve the problem by reconciling conflicting needs. This constructive impulse appeared in the content of the patient's delusions, sometimes in a regressive form.

In estimating the outcome of a psychosis, it is helpful to try to reconstruct the patient's problem in adaptation which the psychosis is attempting to solve and to estimate the possibilities for a successful solution in view of the actual life situation. The destructive impulses—which are much more apparent than the constructive ones—must be estimated on the basis of whether they represent a reaction to an acute but temporary frustration which will discharge itself or whether they produce a vicious circle which leads to more frustration or makes recovery impossible. The constructive tendency to find a solution is hidden behind the destructive trends and may appear only in regressive symbolism.

PEARSON, Philadelphia.

THE ARMY MEDICAL OFFICER LOOKS AT PSYCHIATRY. SAMUEL A. COHEN, War Med. **1**:205 (March) 1941.

Cohen points out that the army medical officer is increasingly aware of his need to know more of psychiatry and mental hygiene in order to render more effective service to his unit. He wishes to obtain from the psychiatrist the following information: (1) How to select mentally fit personnel. It is well known that military life aggravates most existing psychic maladjustments. Soldiers with such maladjustments respond poorly to discipline and learning and are therefore positive factors in lowering morale. This is not true, however, in the case of a man whose maladjustment is the result of insecurity in civilian life, for he may find security in the regimentation of the army. (2) How to detect the organ neuroses, such as the "effort syndrome." (3) How the normal mind makes adjustments to a military environment. The soldier must learn to adjust to the separation from his family, the submission to an entirely new discipline, the change in daily routine, a new occupation, the imposition of new restrictions, in which he can only acquiesce, and the dissolution of all the usual social distinctions. (4) How normal personalities are affected by periods of stress and emergency which may endanger life.

PEARSON, Philadelphia.

PSYCHIATRIC EXAMINATION IN THE ARMED FORCES. KARL M. BOWMAN, War Med. **1**:213 (March) 1941.

Owing to the experiences of World War I, the Medical Department of the United States Army is recognizing the need for a thorough psychiatric examination of draftees. The application of this concept, however, must be made carefully. It is important for the medical profession to recognize and the nation at large to know that the Selective Service System is an attempt to select those men who are best qualified to serve their country in the combat service. The rejection of a draftee does not mean that he is unqualified to serve his country but that he is better qualified to render his service elsewhere than by the duties of a soldier. Both the public and the medical profession need to be educated to the fact that the rejection of a draftee places no stigma on him nor does it affect unfavorably

the civilian morale. The Selective Service System must operate for the greatest benefit of the army, the trainee and the nation.

The army needs men who are best suited for combat service and who can readily adapt themselves to an entirely new method of living and to a different conception of their role in life. The man who does not do well in civilian life is extremely unlikely to do well in the army; as Foch said, "the best soldier is the best citizen."

A trainee may be unsuitable for the new and greater strains of army life but may have made and can continue to make a good adjustment in civilian life and there render valuable service to the nation. This needs to be understood by the nation and by the press lest the trainee rejected for military service be subjected to unreasonable criticism by the community.

Careful psychiatric examination of all draftees will pay the nation financially. The author estimates that it costs the nation over $30,000 for each man who breaks down in the armed forces. He points out that 30 per cent of Canadians returned to Canada during the present war were reported to be mentally unfit.

There are about 5 per cent of draftees who are psychologically unfit to serve in the armed forces. In order that all of these be spotted before being enlisted, Bowman advises more training of draft board physicians in the technic of uncovering psychiatric disabilities. A study of the World War soldiers who broke down revealed that their family histories showed a high incidence of mental and nervous disorders, that many of them had definite mental symptoms at the time of enlistment and that the majority broke down within the first, second or third month of service. The draft boards, therefore, should make a careful inquiry into the family history and obtain whatever data there are about the draftee in the records of hospitals, courts, social agencies, schools, etc. Such data are an important aid in evaluating the stability of the candidate.

During the examination the physician should pay careful attention to the appearance of the draftee, inquire into his school record, his vocational history, his use of alcohol, the occurrence of divorce, residence in hospitals, particularly those treating nervous and mental disorders, and the presence of disturbances of his nervous or mental health.

In cases in which there is any doubt the draftee should be referred to a psychiatric consultant.

PEARSON, Philadelphia.

THE NEUROSES OF WAR. A. KARDINER, War Med. **1**:219 (March) 1941.

Kardiner bases his paper on the study of upward of 1,000 patients with "war neuroses" between 1922 and 1925. Of these, 700 had traumatic neuroses. He attempted to treat about 150 of the latter group and actually carried out intensive treatment on 50. Because of the disruption of life, the suffering entailed and the slight relief the patients obtain, he regards the traumatic neurosis as a serious condition. He states that there is no such entity as a war neurosis but that the majority of the men he saw suffered from a traumatic neurosis acquired under war conditions. There is no evidence that any prewar condition predisposes to the acquirement of a traumatic neurosis and there are no criteria by which potential cases can be excluded. However, stammerers; tiqueurs; persons with a history of convulsive phenomena; those who are "fainty," who cannot stand the sight of blood, who have no tolerance of physical pain, who have a low cardiac reserve or who have certain forms of autonomic disturbances, such as gastric ulcer or mucous colitis, are bad risks. Existing hysteria or compulsion neurosis are not contraindications to military service. It would perhaps be well to exclude from front line service persons with a history of convulsions, stammering, tics, persistent autonomic disturbances, schizoid traits or manic episodes.

The symptoms of a traumatic neurosis are: (1) defensive tics and ceremonials; (2) disturbances of the autonomic nervous system, of most varied types; (3) sensorimotor phenomena, and (4) syncopal or epileptiform phenomena. All these widely varying symptom complexes have the following common features: (1) a character-

istic dream life; (2) certain constant inhibitory phenomena; (3) acoustic hypersensitivity; (4) irritability, and (5) a tendency to outbursts of aggression.

The psychopathologic picture is as follows: It is a basic principle that any activity which fails or causes pain tends to be inhibited, and the neurosis is an attempt to establish an adaptation on the basis of resources reduced by the inhibition. The essential pathologic mechanism is a reflex inhibition which results in a drastic change in the patient's conception of himself and of the outer world. Because the inhibition is a defensive reaction, there must be haste in diagnosis and treatment lest the inhibition become more consolidated. The traumatic neurosis, however, does not tend to become more complicated with the passage of time. Cases in which highly organized defensive rituals are manifested have the best prognosis; those in which syncopal phenomena are evident, the poorest.

The traumatic neurosis must be differentiated from hysteria by the clinical manifestations, the dream life and the character changes; from epilepsy by the presence or absence of the startle reflex, the electroencephalogram and the character of the seizures, and from malingering by the peculiar dream life, the irritability and the outbursts of aggression.

The treatment of the acute stage is prophylactic; that of the chronic state is reeducative. The psychiatrist has an obligation to cure these neuroses or to prevent their development. It is not enough to compensate the patient for his disability. Compensation should be given only in cases of long-standing, intractable disease.

PEARSON, Philadelphia.

Diseases of the Brain

LOCALIZED NONSUPPURATIVE ENCEPHALITIS SECONDARY TO INFECTIONS OF THE TEMPORAL BONE AND PARANASAL SINUSES, WITH A REPORT OF FOUR CASES. JOSEPH C. YASKIN, J. Nerv. & Ment. Dis. **92**:281 (Sept.) 1940.

Yaskin reports 4 cases in which signs of localized disease of the brain followed infection of the temporal bone or the paranasal sinuses. The signs included various paralyses, aphasias, anesthesias or cerebellar dysfunction, with or without evidences of increased intracranial pressure; moderate pleocytosis, and usually restlessness, irritability or delirium. In 3 of the cases mastoid infection was responsible, spreading in 2 cases to the temporal lobe and in 1 to the cerebellum. In the fourth case frontal, ethmoid and maxillary sinusitis was followed by evidence of focal disease of the right temporoparietal region. In this case the pressure of the cerebrospinal fluid was elevated and the cell count 150, with predominance of lymphocytes. All the patients recovered without development of abscess of the brain, after adequate treatment of the original infection. Yaskin states that the pathogenesis and morbid anatomy in such cases are not known and that the diagnosis is difficult, since the condition seems to represent only a stage in the development of an abscess which never materializes. He emphasizes the importance of prompt eradication of the responsible focus of infection and the avoidance of too early exploration of the brain for possible abscess.

MACKAY, Chicago.

HYPOGLYCEMIC EPILEPSY. LEON J. ROBINSON, J. Nerv. & Ment. Dis. **92**:442 (Oct.) 1940.

In reviewing the subject of convulsive states due to hypoglycemia, Robinson points out that low levels of sugar may result from excessive secretion of insulin by a tumor, from functional hyperactivity of the pancreas or from deficient secretion of anti-insulin hormones of the adrenal, pituitary or thyroid gland. Although epileptic patients rarely have abnormal levels of blood sugar and although hypoglycemia artificially induced in epileptic patients usually fails to bring on seizures, the occurrence of convulsions due to hypoglycemia is well established. On the other hand, seizures may be associated with, but not due to, low levels of blood sugar. Attacks of true hypoglycemic epilepsy occur during periods of fasting, often at night; they may be avoided by the preventive ingestion of food and are

preceded by hunger, faintness and sweating. Many other symptoms may occur, such as weakness, restlessness, epigastric pain, nausea, vomiting, vertigo, emotional instability, anomalies of behavior, muscular twitches, stupor and coma. Phenobarbital may effectively prevent seizures. Though administration of carbohydrates relieves the attacks, spontaneous recovery is not uncommon. Since the level of sugar in the blood may be confusingly high at times, it is well to prolong dextrose tolerance tests for six hours and to use exercise in inducing hypoglycemia in such cases. Treatment requires removal of a pancreatic tumor if one is present. Dietary measures include frequent feedings, possibly with low carbohydrate content, since sugars stimulate the production of excessive amounts of insulin. Strenuous exercise is to be avoided. Injections of dextrose intravenously and epinephrine intramuscularly serve emergency needs.

MACKAY, Chicago.

CYSTICERCUS CYST OF THE FOURTH VENTRICLE WITH SURGICAL REMOVAL. LEO ADELSTEIN, J. Nerv. & Ment. Dis. **92**:623 (Nov.) 1940.

Cysticerci rarely appear in the central nervous system, even if distributed generally throughout the body. When they do invade the nervous system they have a predilection for the meninges and ventricles. Adelstein reports the case of a man aged 21, a meat handler in a restaurant, who had suffered from nausea and vomiting for ten days. Examination revealed pallor, weakness and emaciation, violent spontaneous nystagmus, dilated and sluggish pupils, papilledema, with an elevation of 3 D., and ataxia and hypotonia of the right upper extremity. There was no eosinophilia. The cerebrospinal fluid was normal except for a pressure of 250 mm. of water. Cerebellar exploration revealed a solitary cystic mass filling the fourth ventricle like a cast and apparently without attachment. It was filled with clear fluid, and the membranous wall contained single and multilocular daughter cysts and infiltrations of multinucleated wandering cells. After removal of the cyst the patient recovered and was free of symptoms eight months later.

MACKAY, Chicago.

THE MENTAL AND NEUROLOGICAL SEQUELAE OF CARBON MONOXIDE ASPHYXIA IN A CASE OBSERVED FOR FIFTEEN YEARS. NAOMI RASKIN and OWEN C. MULLANEY, J. Nerv. & Ment. Dis. **92**:640 (Nov.) 1940.

Raskin and Mullaney report the case of a woman who was asphyxiated by illuminating gas at the age of 43, when she was four months pregnant. She remained unconscious for four days and apparently recovered, but within a few days began to suffer from insomnia, depression and loss of memory. Miscarriage occurred at the sixth month of pregnancy. Her work as charwoman was poor; she lost weight and became absent-minded and forgetful, restless, irritable and apprehensive. Seven years after asphyxiation there were in addition only coarse tremors, retinal arteriosclerosis and mental obtuseness. She complained of "creepy feelings all over" and "chattering" of her teeth. She continued to deteriorate mentally, became secretive, excessively religious, confused and aphasic. Fifteen years after the accident she was at times mentally disturbed and agitated, untidy, threatening and without insight. Physical findings then included only slight arterial hypertension and arteriosclerosis, slight tremor of the left arm and leg and generally increased tendon reflexes, with ankle clonus but no abnormal plantar responses. Speech was thick, her face masked and her eyes staring. She died of bronchopneumonia, at the age of 58. Autopsy revealed bilaterally symmetric cystic softenings in the globus pallidus and numerous areas of incomplete softening throughout the cerebral cortex. There were regions of demyelination in the white matter and degeneration of ganglion cells in the thalamus, cornu ammonis and cerebellar cortex. Considerable fibrillary gliosis, and even fibrosis in the most severely damaged areas, represented the reaction to the lesions. The authors state that this is the only reported case in which the patient was observed over so long a period.

MACKAY, Chicago.

Congenital Anomalies

CEREBELLAR AGENESIS. H. S. RUBINSTEIN and WALTER FREEMAN, J. Nerv. & Ment. Dis. **92**:489 (Oct.) 1940.

Rubinstein and Freeman report the case of a Negro who had always been subnormal mentally but self supporting since adolescence, and who had shown no evidence of motor dysfunction until the age of 69. At that time he began to fall occasionally. At 72 he was stooped, showed marked incoordination and exhibited sluggish pupils, slurred speech, intention tremor and "athetoid" movements. There was memory defect with vague delusions. Death occurred at 74, of tuberculosis. Necropsy revealed arteriosclerosis, softenings in the left parietal region and numerous developmental anomalies. On the right side there were defects in the superior and inferior colliculi, the trigeminal mesencephalic system, the lateral lemniscus, the medial geniculate body and the vestibular nuclei. Of the cerebellum, only two fairly well developed flocculi were present, which received fibers from the superior vestibular nuclei. There appeared a trace of vermis to the left of the midline and three simple folia of the lateral lobe on the right. Except for some microgyria, the microscopic appearance was normal in the existing portions of the cerebellar cortex. Masses of gray glial tissue were situated at the sides of the fourth ventricle. The roof nuclei were not present, and only a small part of the left nucleus emboliformis was noted. The restiform bodies were thin; the pons was very small, with only a few cells in its nuclei, and the brachium conjunctivum was poorly myelinated on both sides. The red nuclei were small, especially on the left. The inferior olive was of simple formation, with the medial accessory olive poor in cells and the dorsal accessory olive absent. The central tegmental tract was scarcely identifiable, and only thin bundles of myelinated fibers encircled the olive and formed the olivothalamic tract.

Rubenstein and Freeman point out that, except for bilateral cerebellar agenesis, the important neural deficiencies were largely unilateral. Two processes seemed responsible: defective closure of the neural tube on the right and bilateral cerebellar aplasia. The portions of the cerebellum present were phylogenetically the oldest. These simple cerebellar structures sufficed to carry out cerebellar function during most of the patient's life, not because of any compensating mechanism, but probably because the patient functioned "on a lower psychosomatic, social, economic and intellectual level."

MACKAY, Chicago.

LEBER'S PRIMARY OPTIC ATROPHY WITH OTHER CENTRAL NERVOUS SYSTEM INVOLVEMENT. S. ANDROP, Psychiatric Quart. **15**:215 (April) 1941.

Androp reports 2 cases of Leber's disease in which neurologic evidence of other involvement of the nervous system was found. No report of the pathologic changes has as yet been made, leaving an important step in the evaluation of this disease unaccomplished.

The 2 cases reported were those of brothers in a family known to be heavily tainted with visual disorders for three generations. One of the patients had a schizophrenic psychosis. He showed slight tremor of the fingers and hyperactive reflexes in the lower extremities. The gait was broad based and clumsy. The second patient showed progressive speech disturbances, poor coordination, muscular underdevelopment and weakness of the flexor, adductor and abductor muscles of the fingers and toes. There were slight choreoathetoid movements of the tongue and mouth muscles. The deep reflexes were decreased in the upper extremities and hyperactive in the lower. Speech was stammering and slurring. These cases are considered instances of Leber's disease, "a familial abiotrophy of the optic nerve which may extend or be accompanied by degeneration in other parts of the central nervous system."

SIMON, Worcester, Mass.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

SAMUEL BROCK, M.D., *Chairman of the Section of Neurology and Psychiatry, Presiding*

Joint Meeting, March 11, 1941

Effect of Liver Therapy on Pathways of the Spinal Cord in Cases of Subacute Combined Degeneration. DR. CHARLES DAVISON.

The cases of 10 patients who had pernicious anemia with subacute combined degeneration of the cord and who received liver therapy were studied clinically and histologically.

The subjective neurologic symptoms improved in all but 1 case. Improvement in the objective neurologic signs was observed in only 3 cases.

The pathologic process in these cases was not as noticeable and the myelin sheaths and axis-cylinders were not as extensively destroyed as in cases of untreated or mildly treated patients. In 5 of the 10 cases the degeneration, instead of involving the posterolateral tracts, was limited to the posterior columns and rarely invaded the pyramidal pathways. Even in the other 5 cases the pathologic changes were most marked in the posterior columns. In all instances there was a progressive glial change (gliosis), which was most pronounced in the posterior columns. This type of gliosis was not observed in patients with subacute combined degeneration who did not receive liver therapy.

By the early parenteral administration of adequate liver extract cessation and reduction in the swelling of the myelin sheaths can be accomplished, further destruction of the axis-cylinders being thus prevented. The function of the axis-cylinders can thus be restored, provided they are not completely destroyed. This form of treatment also induces glial productivity.

This paper was published in full in the March 1941 issue of the *Archives of Internal Medicine*, page 473.

DISCUSSION

DR. LEWIS D. STEVENSON: In his paper tonight, and in his previous article, Dr. Davison has demonstrated an interesting phenomenon, namely, the production of noticeable gliosis in the cords of patients with pernicious anemia if the blood picture is restored to normal by liver therapy. The patients also improve subjectively, to some extent, and even on examination they may show certain improvement. The gliosis that occurs with treatment is due, I think, to the more adequate blood supply. It has been my observation that wherever in the brain or spinal cord the blood supply is not good astrocytes cannot proliferate. Even more than the neurons, these cells require blood and oxygen—plenty of it—in order to produce a scar.

Two factors are concerned in the improvement that these persons show: They are very weak, and even fainting and unable to walk, because of the great general debility rather than involvement of the pyramidal tracts. When the red cell count is increased again to 5,000,000 or so, they recover from this weak, fainting condition and are able to walk. I have seen that happen several times in cases of acute weakness and ataxia of the legs. For a long time I overlooked the presence

of peripheral neuritis in addition to the lesions in the spinal cord, a fact that has been demonstrated adequately by two papers. Hamilton and Nixon (Sensory Changes in Subacute Combined Degeneration in Pernicious Anemia, ARCH. NEUROL. & PSYCHIAT. **6**:1-31 [July] 1921) showed clearly that there is degeneration of the peripheral nerves and posterior roots and stated: "Contrary to the generally expressed opinion, degenerative changes in the peripheral nerves are common in pernicious anemia and constitute an important part of the pathological anatomy of that disease." The process is reversible, and probably is due largely to vitamin deficiency; when this is corrected, particularly if one uses a substance like lextron, a stomach-liver concentrate which contains in addition the vitamin B complex, the paresthesias and other signs of peripheral disease may all disappear.

Formerly Dr. Greenfield (Buzzard, E. F., and Greenfield, T. G.: Pathology of the Nervous System, London, Constable & Co., 1921), in discussing subacute combined degeneration, stated "The spinal roots and peripheral nerves are healthy." For a long time this was taught, but later Greenfield and Carmichael published a paper (Peripheral Nerves in Cases of Subacute Combined Degeneration of the Cord, *Brain* **58**:483-491 [Dec.] 1935) in which they retracted that statement. They said that in a comparative study of peripheral nerves from normal persons, from patients with subacute combined degeneration of the cord and from patients with neuritis, it has been shown that the myelin sheaths are reduced in number in patients with subacute combined degeneration and that the reduction is of the same type, though not of the same degree, as that in alcoholic persons. I think, therefore, much of the disappearance of the objective signs of disease is due to the regeneration of the peripheral fibers, in the arms and particularly in the legs. As far as I can learn from Cajal's latest work on degeneration and regeneration in the central nervous system, there is no successful regeneration of neurofibrils in the spinal cord or brain. There is only an abortive attempt at regeneration; so pathways in the spinal cord cannot possibly be reestablished.

The Psychopathology of Psychopathic Personalities. DR. GEORGE S. SPRAGUE, White Plains, N. Y. (by invitation).

The concept of the psychopathic personality has been developed since 1893 on a behavioral, or characteriologic, basis. The best statement is that of Kurt Schneider, that psychopathic personalities are those abnormal personalities who suffer from their abnormality or from whose abnormality society suffers. In this paper, instead of accenting community interest or the individual's reactions to his condition, I wish to investigate the inner psychobiologic state of the psychopathic personality. Investigation of such a personality reveals at least nine aspects of the psychopathic reaction, some or all of which are invariably present: (1) inability to postpone; (2) ineffective consideration of consequences; (3) insufficient learning from experience; (4) faulty synthesis; (5) disproportionate responsiveness; (6) affective dominance over intellect; (7) disvaluation of reality; (8) disregard for truth, and (9) insufficient social evaluation.

It is concluded that the mental processes of the psychopath appear to act in a less mature fashion than those of the ordinary person. In the absence of any demonstrated neuropathologic basis, this must be considered a behavioral deviation. It therefore follows that dynamic explanations of the phenomena should be sought. In considering various individual traits among the nine mentioned, it appears that the psychopathic person gives exclusive or preponderating attention to one or a few factors, thus excluding others which should also receive consideration. Here is an improper ascendancy or an overvaluation of certain material. This accounts for the lack in validity, in adequacy and in accuracy of the psychopathic response. It is evidently the purely personal significance of material that demands the psychopath's first attention, so that he remains fundamentally an individual rather than a social being. Egocentric notions continue, as

in childhood, to have predominating importance over impersonal, or generalized, material. The psychopath reacts to details because of their emotional value rather than because of their reality or factual significance. To the psychopath he himself is the center of the universe. From his essentially narcissistic viewpoint, whatever is outside of the focal point, himself, is tacitly excluded. Realities are not distorted but have, for the psychopath, an individual, personal set of values which makes them hold different implications from those of other people, thus leading to unusual associations and behavior. It is not proper to judge the reactions of the psychopathic personality on the basis of their relation to the outer world of reality. It is the psychopath's inner balance of affective and instinctive urges of the moment which determines his behavior, rather than the actual situation in which he finds himself, by which latter standard one is accustomed to measure his adequacy.

The view is set forth that the psychopathic personality has a fixation in psychic development. It consists of an enduring restriction of the affective attachments such that significance or motivating value does not widen its scope to include as much of the world of external reality as is usual in adult life. It is an enduring tendency to measure by a personal, rather than a social, yardstick.

DISCUSSION

DR. KARL M. BOWMAN: Dr. Sprague has given an interesting description of the psychopathic personality, and in his summary he has emphasized the essential infantilism of such a personality. Since I feel that this is the crux of the situation, I should like to develop this subject a little further. One thinks of persons as born with certain latent capacities which may or may not be completely developed. These capacities may be in the intellectual sphere, or they may be in other spheres. If a person's intellectual capacities do not develop to the extent that those of the normal person's do, one commonly speaks of him as feebleminded, or mentally defective. There are three factors which, alone or combined, may cause his feeblemindedness: He may be born intellectually defective because he has inherited this defect from his ancestors; second, he may have been born with suitable capacities for development, but some organic factor, such as an injury to the head or encephalitis, has prevented his development; third, psychologic factors may interfere to a marked degree with this development. For example, a short time ago my associates and I at Bellevue Hospital had brought to us a child from the pediatrics ward who was regarded as feebleminded, who did not talk or walk. He had had a series of illnesses and had received excellent pediatric care, but no other type of attention. No one had talked to him, or been affectionate toward him or encouraged him to develop, and therefore the normal capacities had not developed. With careful training they soon developed. It is my opinion if the child had been left in that way for a certain period a stage would have been reached at which he would have been unable to develop in the normal fashion, and thus the psychologic effects would have persisted.

The psychopathic personality is one which has failed to develop in the normal adult fashion, in the nonintellectual attributes. It seems to me that most of the traits Dr. Sprague spoke of are those which one would call part of the normal behavior of the infant. For instance, the small child is self centered and egoistic, narcissistic, if you like, and it is only as he grows older that he acquires an attitude toward the community in which he lives which is regarded as that of the normal adult. One expects a small child to be explosive and overexacting; as he grows older he acquires emotional control.

As to the difference between fantasy and reality: The small child tells fantastic stories; he is called bright, and his elders are pleased with them. If he persists in such fantasies as he gets older he is called psychopathic, and the fantasying is spoken of as pathologic lying. He has never learned the clearcut

differentiation between fantasy and reality, as does the normal adult. The lying of the psychopathic personality is poorly timed. It does him no good. One calls it abnormal lying. One speaks of normal lying when it is done for some purpose; a man "lies like a gentleman" to protect the honor of a woman. The psychopathic person often lies when no useful purpose is served, and even when he harms himself.

The difference between "mine" and "thine"—property rights—is something which every one has also to learn to recognize. The small child wants what he wants when he wants it; he gets hungry and howls, and every one says what a fine child he is and what a fine pair of lungs he has, but the same behavior in the adult is called psychopathic. One could go on with all the other traits—such as the attitude toward sex.

It seems to me that the psychopathic personality, like mental deficiency, comes about in three ways: It may have a hereditary basis. I agree that one cannot demonstrate or prove this, but it is my opinion that at times emotional instability, or some defect in the emotional makeup of the person, may be inherited, just as much as an intellectual defect. A child may have inherited a normal personality, but a birth injury or a disease of the nervous system may alter it. Encephalitis is the most typical example of a disease in which the personality of a child may be completely changed, and yet his intellectual functions not be affected. I suggest that there are probably thousands, if not millions, of cases of mild encephalitis which are never so diagnosed. Some claim that every one has the disease at some time in his life, but that the attack is so mild that in the majority of instances it leaves almost no residuals and is never diagnosed. If this is so, there must be thousands of persons in whom there develop mild personality changes which are never recognized as being due to organic disease of the brain. Recent electroencephalographic studies have shown that some of the difficulties encountered in so-called normal children may have an organic substratum.

The psychologic factor is familiar to all. A child who has the capacity to develop into a normal personality may develop into a warped one as a result of poor environment and emotional conflicts. The process may reach a stage at which it becomes irreversible, and the so-called psychopathic personality results.

It seems to me that this way of looking at the psychopathic personality, like the feebleminded, is the most satisfactory one has.

Dr. A. A. Brill: Many years ago, when I was still young, Dr. L. Pierce Clark, then president of the New York Neurological Society, asked me to read a paper on the psychopathic personality. I was still at that stage where one naïvely rushes in where angels fear to tread; so I immediately accepted the invitation. Somehow I got sick, and I did not read that paper. At that time there was little interest in psychosomatic medicine; so it did not occur to me that my malady had anything to do with the task before me. Since then I have often thought that there might have been some unconscious insight behind my illness which prevented me from reading that paper on psychopathic personality. I feel so because I never cared to take up this difficult subject, although I still have my notes on it.

Dr. Sprague described the psychopathic personality in an able and interesting manner; he mentioned a number of the authors who have written on the subject and then elaborated on nine of the principal psychopathic reactions. Some of the authors mentioned by Dr. Sprague were really reluctant to speak about a psychopathic personality. Thus, Bleuler spoke of the psychopathies, which he defined as "psychic deviations from the normal, which do not give the impression of pronounced insanities"; he added that it is incorrect to say that the psychopathic person has symptoms that are strictly limited to himself, and pointed out that any delineation of the psychopathic personality is purely artificial. Kahn, who has written a book on the subject, and others are just as careful about the limitation of the psychopathic personality. Nevertheless, every quality mentioned by Dr.

Sprague and his able discusser, Dr. Bowman, is undoubtedly found in some so-called psychopathic personalities. Dr. Bowman seemed to gather from Dr. Sprague's statements that the psychopath is preponderantly infantile; he is intellectually immature because he never develops normally. Still, I have seen a great many people whom one could readily call psychopathic who are intellectually highly developed. Bleuler stressed the emotional elements of the psychopathies, the affectivity, and stated that it makes no difference whether such a patient is of normal or of above average intelligence.

Dr. Sprague's excellent description of the psychopathic reactions reminded me of a paper written not long ago by Maurice Levine, who, too, tried to solve this problem. Levine, using different expressions, gave practically the same characteristics as those enumerated by Dr. Sprague. Thus, what Dr. Sprague termed "the inability to postpone" Levine called the tendency to live by "short term values," or by the pleasure principle. In the ultimate analysis, both of these expressions signify that the psychopathic person lives by the omnipotence of thought, which is so characteristic of the child. The latter wants to realize all his wishes as soon as he becomes aware of them. This also agrees with Dr. Bowman's idea of infantility. So-called psychopathic persons frequently show this trait, but I can think of many others, not at all psychopathic, who evince the same characteristic. One must not forget that at different periods of one's life one shows different emotional reactions. And if one accepts this type of emotional reaction as a guide, then almost every child and every young person could be thought of as psychopathic. I saw today a man whom I consider quite normal. I saw him fifteen years ago, when he was a sophomore at Harvard. His father brought him to me because he was crazy to marry a burlesque girl whom he had met only shortly before. He wanted to leave college, go to work and marry the girl. The father, who was a broad-minded person, having been analyzed, wanted to know what to do about it. In view of the whole situation, I concluded that I was dealing with a psychopathic personality: I felt that this young man was guided by the omnipotence of thought, regardless of his former strong convictions that he wished to go through college. I finally got him to postpone the marriage until the end of the term. I was guided by the assumption that time cures everything, even that sort of malady. Well, he finished the semester and continued until he graduated, and never married the girl. He is now married to a woman of his own type, and, naturally, I changed the diagnosis of psychopathic personality.

With respect to Dr. Sprague's illustration by which he shows the difference between the psychasthenic person, whom it takes hours to buy two neckties, and the psychopath, who simply steals them: These two different types of reaction are generally recognized, but it also recognized that two entirely different types of personality reactions are involved. Dr. Sprague knows that as well as I do. In fact, I feel that neither Dr. Sprague nor any of those who have occupied themselves with this subject before him have succeeded in giving a definition of the psychopathic personality which is in any way all inclusive. To be sure, there are persons who are not psychotic or neurotic or feebleminded but who solve their conflicts in the manner described by Dr. Sprague; in my experience, however, they belong to those borderline personalities which are simply badly put together; yet, in spite of a potential psychosis, these persons can somehow maintain themselves. Those whom I have seen were all constitutionally burdened; some gave vague histories of former disease of the brain (as stated by Dr. Bowman), and, above all, they all showed an affective lability. But one must not forget that emotional disturbances are characteristic of all the psychoses. Stransky has demonstrated long ago that dementia praecox shows a disproportion between the noopsyche and the thymopsyche, and Kraepelin stressed from the very beginning that schizophrenia is characterized by an emotional deterioration. It is also known that emotional disturbances are in the foreground in manic-depressive psychoses. Therefore the affectivity cannot be considered the most important criterion of the

psychopathic personality. Such a personality does not show any stable picture. In fact, as soon as Dr. Sprague asked me to discuss his paper I tried to find out how many people I had diagnosed as psychopathic. I found about 5 in thirty years' experience. In 1 case I had a question mark after the diagnosis. To be sure, I made this diagnosis more often before Dr. Clark asked me to read that paper. Since then I could find no psychopaths. To me, the psychopathic state represents something more definite; it may not be pronounced schizophrenia or a pronounced manic-depressive psychosis, but in most cases it belongs to one of these types. In the effort to make a diagnosis, one usually thinks of the extreme abnormal, or psychotic, state, or the so-called normal, forgetting that between those two extremes there are hundreds, and probably thousands, of gradations. Kretschmer's concept of schizothymic and cyclothymic, which Bleuler prefers to call schizoid and syntonic, has done much to bridge the gap between psychotic and the so-called normal, but above all it shows that more than either schizophrenia or the normal is to be considered. It is my opinion that all the psychopathic personalities belong to some psychotic group and should be classified accordingly. Kraepelin was probably right when he said that a psychopathic personality represents a circumscribed inhibition of development, in contrast to the oligophrenic type, which shows a general inhibition of development. But, whether one follows Kraepelin, Bleuler, Kahn or any of the other authorities, it is impossible to say "This is a psychopath" or "This is not a psychopath." Every so-called normal person shows the same traits in more attenuated form, and hence every so-called psychopathic personality must be studied to determine to what extent his condition is schizophrenic, manic, epileptic or organic.

Nevertheless, I was much impressed by Dr. Sprague's lucid paper. I admire his courage and scientific honesty which prompted him to formulate and classify psychopathic states, which have long puzzled psychiatrists. However, it will take a long time before one can say that there is such an entity as the psychopathic personality.

Dr. Karl A. Menninger, Topeka, Kan.: I want to take the liberty of being somewhat more critical than Dr. Brill and Dr. Bowman. I must say that I think this paper is seriously faulty, and I shall say why I think so.

What is the "psychopathic personality"—a maladjustment, a disease or a personality? Let us as psychiatrists not go up into our ivory towers and say that we are physicians, that this is an old diagnostic category defined in Germany years ago, that we know it means a certain type of inadequate, incomplete, disorganized personality and that others do not need to understand it or criticize its vagueness. At our clinic my associates and I do not use the term at all. I do not know what it means. I *think* it means that in the days when they were not quite clear about what they were trying to diagnose—the personality of the patient or the kind of maladjustment that the patient got into—it was a compromise catch-all category for undiagnosed personality defects.

When talking about certain chronic personality disorders, let us describe them in words that every one understands. Let us say that a person has a moody personality or a criminal personality or a perverse personality or a neurotic personality and define these. Let us use English words that mean something to every physician, instead of words that do not mean the same thing to all psychiatrists, as is evident from the discussion tonight. This is extremely important, for the question of draftee exclusions is occupying the attention of medical men all over the United States. If in the New York Neurological Society and in this Academy there is such diverse opinion as has been expressed regarding this category which Dr. Sprague describes—which I do not think exists and which Dr. Brill has seen five times in thirty years—there will certainly be confusion among the medical examiners who must come to practical conclusions about thousands of applicants after too brief an examination. Errors in their conclusions will cost the nation many millions of dollars. If I have seemed sharp

in my remarks, I trust Dr. Sprague will appreciate that they are directed more at a term for which he is not responsible than at his scholarly discussion of it, taken at its face value.

DR. E. D. FRIEDMAN: May I say that I am not quite in accord with some of the psychoanalysts, and I should like to break a lance for Dr. Sprague. All know that there is no such thing as absolute normality. There are all sorts of gradations of normal behavior, as Dr. Brill has said, but most neuropsychiatrists who have practiced for any length of time recognize certain persons whom they classify as psychopathically inferior. Such persons are those who do the things that Dr. Sprague has spoken of, namely, refuse to subscribe to the mores of the race, and they create problems for themselves and for the rest of society. It is important that this deviation from the normal be recognized early in life and, in doing so, an attempt to find an approach to and method for the disposition of these persons be made. Hitherto, the law has made it impossible to deal with these persons. They are not legally psychotic, but they are sufficiently abnormal to disturb the social atmosphere in which they live. I think all should thank Dr. Sprague and Dr. Bowman for adding their mite to the clarification of this problem.

DR. C. P. OBERNDORF: One of the first bits of research I did was on psychopathic constitutional inferiority (Constitutional Inferiority and Its Psychoses, *J. A. M. A.* **58**:249-252 [Jan. 27] 1912). As the years went on, I was inclined to abandon the term, in sympathy with the psychoanalytic school in its aim to determine the dynamics producing mental conditions. Recently, I have been examining men in the selective draft, and there I have come in contact with types of personality constitutions which I rarely saw in private practice or in the public psychiatric clinics—persons who come out from the cellars, from the back rooms; odd persons, not depressed, not introverted, not moronic; persons whom it is difficult to classify under any of the accepted categories. Some might be classified as emotionally immature and some as emotionally unstable; others show anomalous deviations. If one is to separate them into classes as the government now requests, the term psychopathic inferiority seems to fit the condition better than any other. It seems to me there are a great many such people whom one recognizes as differing decidedly from anything which one can call the normal or from a full-fledged psychotic condition, for whom the term psychopathic inferiority tells the story better than anything else available at present.

DR. LEWIS D. STEVENSON: I am only a neuropathologist, but I should like to add my opinion to that of Dr. Sprague and Dr. Friedman. I think this term, although it is difficult to define, means something; it means a certain type of personality, which Dr. Sprague has described and has tried to analyze; I think he has been most lucid about it, and so has Dr. Bowman.

DR. GEORGE S. SPRAGUE, White Plains, N. Y.: I want to thank the discussants for adding thoughts and interest to the topic presented. Dr. Bowman has correctly stressed that whatever may be the cause of these conditions, it is the resulting picture that must be dealt with and that this picture seems to be properly regarded as a form of immaturity.

I accept readily Dr. Brill's statement that many people who are not to be called psychopathic have the traits found in psychopathic persons. The issue is one of gradation, with every one having all of the traits that every one else has; the question is how the balance is maintained. A psychopathic balance is assumed to mean that one has a psychopathic personality.

The question Dr. Menninger raises is one which troubled me in trying to justify the title of the paper. What I meant was this: When one speaks of a "psychopathic personality" one is talking descriptively, from the outside; by "psychopathology" I wished to call attention to the inward facts of the situation, to designate the psychologic makeup of the person, not whether he was riding freight cars or stealing watermelons. But in the discussion tonight, at least every one knew what I was talking about.

Ambulatory Schizophrenia. Dr. Gregory Zilboorg.

The concept of schizophrenia is reviewed historically. All three present day systems of psychopathology (those of Kraepelin, Bleuler and Freud) have used as their point of departure the associativistic psychology of Wundt. The nosologic differences in the three systems are based primarily on their respective attitudes toward prognosis, affectivity and ideational content. The last was described as the only reliable differential point, and the relation between object concept and word was stressed as particularly conducive to early recognition of schizophrenia.

Ambulatory schizophrenia is real schizophrenia which is slow in developing and abounds in definite characterologic traits. The patient is amenable to psychotherapy, particularly psychoanalysis. Hospitalization is seldom, if ever, necessary —hence the appellation "ambulatory." The term is suggested not as a designation of a possibly new nosologic variety, but as a descriptive name only. From the standpoint of psychodynamics and inner phenomenology, it is an early form of schizophrenia.

DISCUSSION

Dr. A. A. Brill: One can only touch on some of the high spots that Dr. Zilboorg gave in this interesting paper. I appreciated it very much because, as he said, I have in a way lived through the whole course of development of the concept of schizophrenia. I started with Meyer, took a course with Kraepelin and then worked with Bleuler. I wished to be Kraepelin's translator long before I became Freud's, but he wrote me that he already had one. Years later, when he was in New York, on his way home from his trip to the Orient, he would have been pleased to have me become his translator. I told him that as I had just given up translating Freud, it would not do to start any other translations. But I was always interested in schizophrenia; the first money I earned as a physician I spent on buying Kraepelin's textbook, and my first knowledge of psychiatry came to me from Kraepelin via Meyer. Hence, everything in Dr. Zilboorg's paper affected me, I might say, emotionally.

Apropos of what Dr. Zilboorg said about Bleuler, I should like to add that Forel exerted a great influence on Bleuler. Forel, as most of you know, was not only a great psychiatrist but also a naturalist of no mean ability. He was especially interested in ants and wrote numerous books on them. With Kraepelin, he was the founder of the antialcoholic movement in Europe and also started such a movement in this country. Later, when the American antialcoholic movement became identified with religion, Forel gave up his association with it. Forel was a versatile person, whom Bleuler emulated in many ways. Another reason for Bleuler's interest in schizophrenia may be the fact that his sister was catatonic. He never sent her to a hospital, but kept her in his home. Schizophrenia, as it were, became a part of his daily life.

Having been, as it were, reared in Kraepelin's psychiatry, I was extremely impressed when I came to Bleuler; everything was so new and so stimulating that I felt like a fish put back into cool, clean water. For after I had worked for about five years with descriptive psychiatry, I lost almost all interest in it. I thought of giving it up and becoming a nose and throat specialist. Despite Kraepelin's great service to psychiatry, his descriptive approach to the psychoses, especially dementia praecox, resulted in a feeling of hopeless monotony, which grew proportionately with time. In Burghölzli I became acquainted with Freud's new concepts, which not only injected interest into the psychoses, but also opened new vistas for further research.

I fully agree with Dr. Zilboorg's broad implication of the term schizophrenia and the role of affectivity in the morbid process. I could confirm his statements by many examples, but I shall give only a few. Dr. Zilboorg mentioned the lack of affectivity of a certain murderer. I spent many hours with this man when I examined him for the state. Among other things, I once asked him whether

he ever went out with women. He said that he used to go regularly, whenever he had a chance. I asked him how often he went, and he said, "When I had money, every week, and sometimes twice a week." I then asked him, "Why did you have to attack the woman you killed and get into this mess? Why didn't you get a prostitute?" "You know," he answered, "I am engaged to a very nice girl, and I could not go to whores." His answer nicely demonstrates his schizophrenic affectivity, a type of affectivity which is common to all schizophrenic persons.

I am also convinced that for accessible patients psychoanalysis is the best form of psychotherapy. I have been analyzing such patients from the very beginning of my freudian career. Indeed, the first analyses I made were of patients with schizophrenia. I agree with Dr. Zilboorg that one usually gets such patients when the disease is in the terminal stage. Only occasionally does one get the patient before the schizophrenic process is flourishing or when he is still intact enough that one can warn the parents of the coming disintegration. I am convinced that if the patient can be analyzed in the incipient stages, he can be helped. The therapy, as Dr. Zilboorg said, consists in bringing about an affective integration in the patient. It is not easily accomplished, but it is fascinating to watch the process.

In this connection I wish to mention a patient who has been ill since 1905. When I first saw him, I thought he had a compulsion neurosis, but even then he was not a case for regular analytic therapy. I then saw him at infrequent intervals, sometimes after a lapse of years. In 1928 he showed typical schizophrenic disintegration, but as he had some insight into his condition, I advised him to go to a hospital. I sent him to a state hospital, where he stayed for a while and seemingly improved. The schizophrenic process, however, could not be stopped, but because of the insight instilled into him by the physicians inside and outside the hospital, he has been able to keep more or less in contact with reality. While he was in my office this morning he showed in an interesting way the splitting of his personality. While talking to me he would suddenly scream to the voice, or "the child" within him, which he designates as "he." After such an interruption he remarked, "You see how he fights with me. He says he wants me to do this, and I do not want to do it." "Doctor," he said, "years ago you told me to pay no attention to him, and I do that, but he won't let me sleep." This patient is almost constantly struggling with his split-off part; yet he has maintained himself outside of a hospital for many years.

I have known a number of patients with similar more or less split personalities, some of them I took out of hospitals twenty-eight years ago and who have been able to maintain themselves fairly well with a little help. Some have made good social adjustments.

A few words about the schizophrenic associations. One of my women patients, who was also seen by Dr. Kirby and Dr. Potter, insisted on calling me Dr. Hill, despite the fact that she knew my name and was corrected whenever she called me "Hill." I explained her mistake by the sound association of Brill and Hill. In addition to calling me "Hill," she invariably asked me, "Where is your red carnation, Dr. Hill?" Whenever she saw me, she would say, "Hello, Dr. Hill, where is your red carnation?" I found then that "Brill-Hill" was not just a chance association and that she really thought of some one else, with whom she identified me. She thought of Dr. A. A. Berg, the famous surgeon, who had operated on her some years before. Dr. Berg has the same initials as I, and some who know Dr. Berg will recall that he is in the habit of wearing a red carnation.

I am citing this as a typical schizophrenic association, to demonstrate that no matter how strange such associations may sound, they nevertheless show good logic when analyzed.

As I said, it is not easy to discuss a paper of the type presented by Dr. Zilboorg. All I can say is that I fully subscribe to what he said about this complex problem,

and I have merely added a few clinical examples by way of illustration. In closing, I wish to repeat that I thoroughly enjoyed this stimulating and characteristically zilboorgian presentation.

DR. C. P. OBERNDORF: This subject of ambulatory schizophrenia is not particularly novel. In 1911 Dr. Jelliffe (Pre-Dementia Praecox: Hereditary and Constitutional Features of the Dementia Praecox Make-Up, *J. Nerv. & Ment. Dis.* **38**:1, 1911) presented a stimulating paper which expressed many of the thoughts given tonight. But the point which I am raising is this: Has not Dr. Zilboorg fallen into the error which he inveighed against at the outset of his paper, namely, classifying a certain form of the disease as ambulatory schizophrenia, which is quite as definite a classification as constitutional psychopathic inferiority? Is it not true that many of the cases he has cited as instances of incipient schizophrenia might have been classified as those of constitutional psychopathic inferiority without extending the scope of this term?

In other words, there has not been great advance in the understanding of this group of conditions in which queer conduct oddities, associational difficulties and lack of affect are observed, which formerly were classified as psychopathic inferiorities and which now Dr. Zilboorg would group as ambulatory schizophrenia.

One other thing I should like to mention: In the examination of the population, as has been demonstrated through the draft, one finds a great number of men much in need of mental classification and psychiatric help. Many of them defy more accurate diagnosis than constitutional psychopathic inferiority. If an act similar to the draft could be extended to women, as a matter of stock taking, as a matter of investigation of the health, mental and physical, of the female population, I am sure that it would reveal a great number with ambulatory schizophrenia.

DR. GREGORY ZILBOORG: I wish to thank Dr. Brill and Dr. Oberndorf for their discussion: Dr. Brill for his nice approval and understanding and Dr. Oberndorf for his nice misunderstanding. Dr. Brill's reminder of the influence which Forel had on Bleuler is particularly apt; I was not unaware of the fact. But this influence was more of a personal nature, and to my way of viewing the historical development of the concept of schizophrenia, Forel did not help Bleuler in the latter's scientific orientation.

The reproach that I try to introduce a new classificatory label is not justified. I dislike classifications. A classificatory confinement makes me feel claustrophobic. I used here the word "ambulatory" in its etymologic sense only, and designate by it the schizophrenic persons who walk about and seemingly require no hospitalization.

PHILADELPHIA PSYCHIATRIC SOCIETY

LAUREN H. SMITH, M.D., *President, in the Chair*

Regular Meeting, March 14, 1941

Hereditary Patterns in Involutional Melancholia. DR. HAROLD D. PALMER and DR. FREDERICK J. JARDON, Philadelphia.

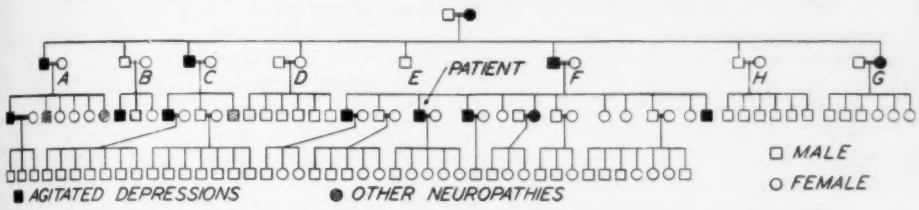
The total life course of a patient with involutional melancholia has been shown to possess a highly characteristic psychobiologic fixity. This pattern of the personality in all of its attributes bears the stamp of rigidity and control. The prepsychotic personality of involutional melancholia appears to have a more characteristic and homogeneous design and bears an even more specific relation to the psychosis than the cyclothymic pattern bears to manic-depressive psychosis. The psychotic breakdown occurs in this type of personality under the impact of the numerous stresses of this life period (Palmer, H. D., and Sherman, S. H.: The

Involutional Melancholic Process, ARCH. NEUROL. & PSYCHIAT. **40**:762-768 [Oct.] 1938). Strikingly revealed throughout our study of the illness is the patient's repetition of a life course and psychotic reaction identical with that of a parent or affected sibling. The presence of a constitutional factor in the illness is undoubted, but the extent to which hereditary factors account for the psychosis or for its symptomatology has not been clearly presented. As part of an attempt to evaluate the constitutional and hereditary components, we wish to present a striking case together with the genetic chart. In our total study this case history and record of the siblings and antecedents have numerous counterparts.

Positive heredity in mentally ill patients has been found generally to approximate 40 to 50 per cent, in contrast to less than 10 per cent in the general population. Farr, Sloane and Smith (*J. Nerv. & Ment. Dis.* **71**:36-44, 1930) compared the data on heredity in 75 cases of involutional melancholia with those in 100 cases of manic-depressive psychosis at the Pennsylvania Hospital and found positive hereditary factors in 27 per cent of the involutional group, as compared with 40 per cent in the manic-depressive group.

REPORT OF A CASE

Personal History.—A man aged 59 was admitted to the Pennsylvania Hospital in 1940, presenting symptoms of a severe depression, marked anxiety and agitation, self accusation, hypochondriacal trends, somatic delusions, feelings of hopelessness



Genealogic chart showing occurrence of involutional melancholia in three generations of a family line.

and despondency. The illness had been present in its psychotic form for approximately four months before admission. The prodromal period, of approximately one year, was characterized by a slight decline of energy, a reduction in business efficiency and gradual withdrawal from social and business contacts. The past personal history indicated that he had had no previous depressions or mood swings and that he had always been considered a meticulous, somewhat opinionated and domineering man, interested only in his work. The prepsychotic personality pattern and the psychotic symptoms were those of classic involutional melancholia. Recovery occurred promptly after electric shock therapy.

Family History.—There was a strong saturation of the entire family line, over three generations, with involutional melancholia. Almost all of the ancestors were successful in a business sense but showed evidences of irritability, narrowness of vision and egocentricity to a marked degree. Visible throughout was a fairly consistent pattern of rigidity.

The first affected member of the family line shown on the genealogic chart was the patient's grandmother, in whom a mental illness characterized by depression, agitation and anxiety developed at about the age of 45. It is not known whether she was confined to an institution. She recovered after several years of medical treatment, said to consist of extensive bleedings. According to biologic law, it is necessary in order that a mendelian recessive characteristic appear in the next generation that a taint be present in the partner of the affected person. Then 50 per cent of the offspring will show the original pattern and the other 50 per cent will carry the taint. Just how specifically this works out in a family

line is shown in family *A*, in which involutional melancholia appeared in a member in his late fifties. This patient died after six years of illness. Of the 6 offspring, the eldest had involutional melancholia at the age of 58, was ill more than two years and then made a complete recovery. The second died in status epilepticus at the age of 26. The rest were well, except for the youngest, who is classified as intellectually retarded.

In family *B*, it would be expected that the father, although he did not have a mental illness, would carry the characteristic and that, given a tainted partner, one quarter of the children would show neuropathic evidence. It is seen that 1 of the children had typical involutional melancholia in his late fifties, and died after several years of illness.

In family *C*, involutional melancholia terminated fatally in a patient aged 59. If the wife carried a neuropathic taint, one would expect 50 per cent of the offspring to exhibit a psychopathologic condition. The eldest son had involutional melancholia, at the age of 56, but recovered at 61. The second son had onset of schizophrenia in his early twenties and has remained ill. The third is normal, but theoretically should carry the recessive characteristic.

In family *D*, one would expect that the characteristic would be carried in the protoplasm but that, given a partner free from taint, all the offspring would be normal. This seems to have been the case, as shown by the chart.

In family *E* the situation is essentially the same.

In family *F*, the father of the patient whose case is reported first had involutional melancholia at the age of 58. He recovered after nearly two years of institutional treatment. One would expect that if his wife carried a recessive characteristic 50 per cent of their offspring would show mental disease; as is shown in the chart, this was the case. In the eldest, a man, involutional melancholia developed at the age of 58 and he died after fourteen months. The second, a man, now is living and well, at the age of 64. The third, a man, is the patient. The fourth, a man, is now ill with involutional melancholia and has been in a hospital for mental disease for three years. The fifth, a girl, died at the age of 19, of typhoid fever. The sixth, a woman, had involutional melancholia at the age of 45 and died in a hospital for mental disease after two years of illness. The eighth, a nun, is living and well and is the leader of her convent. The twelfth, a man, has recently recovered from involutional melancholia. The seventh, a man, died accidentally, at the age of 40. The ninth and eleventh children, both girls, died in infancy. The tenth, a man, has had no mental difficulties to date. Interestingly enough, there have been no suicides in the family.

In family *G*, 1 woman had involutional melancholia in her late forties and recovered after one and one-half years of institutional treatment. One would expect that, given a normal partner, there would be no mental disease in the offspring. This seems to have proved true, as is shown by the chart. However, all offspring should carry the characteristic.

Family *H*, as far as can be learned, has been and is entirely normal.

Among the 51 persons in the first three generations, there were 13 cases of typical involutional melancholias, 1 of schizophrenia and 1 of epilepsy.

Repetition of this unfortunate record in the fourth generation can be anticipated if the hereditary influences continue to operate in the mendelian sense. A large majority of the members should carry the recessive characteristic. Whether or not there is overt mental disease, however, should theoreticaly depend on the partner's biologic stamp. If the partner's heredity is normal, the characteristic is merely passed on to the succeeding generation.

Although this is the record of only one family in which involutional melancholia appeared, it shows with remarkable clarity the application of the theory of mendelian recessive characteristics and also is a typical illustration of the behavior of other hereditary patterns in our study. There is more than a strong suggestion of a positive hereditary influence in involutional melancholia.

DISCUSSION

DR. HAROLD D. PALMER: One of the points which can be made, especially with regard to the inheritance of involutional melancholia, is that the disorder and its distressing symptoms are largely attributable to the superego, and the superego is believed to be a wholly acquired portion of the psyche.

There can be no question regarding the fixity of the lifelong personality of involutional melancholia, with its highly inhibited, strongly repressed, rigid characteristics. Likewise, the operation of an overdeveloped superego in the prepsychotic personality and in the acute mental suffering characteristic of the psychotic phase cannot be doubted. If the illness is to be looked on as purely psychogenic, it can be acceptably explained as the breaking loose of a highly punitive superego. The superego can be quite acceptably explained as a wholly acquired portion of the personality. However, many persons possessing the obsessive-compulsive character traits and having similarly overstrong and harsh superego development go on through life, even through the involutional stresses, without psychotic catastrophe.

It has been interesting to consider the effect of changing cultural influences on the qualities of the superego. Certainly, the cultural factors over a period of the century covered by this family appear to be those tending toward greater emancipation from parental domination and toward reduction of the force of the moralistic rigidity and control. It would seem, therefore, that the overdeveloped features of the superego ought to die out with the opposing mitigating influence of emancipation, loss of respect for elders, "enlightened" relaxation of the domination by parents and lessening of the rigidity of moral codes. This favorable modification does not appear to have occurred during the life course of successive generations of this interesting family. Therefore, it would seem all the more likely that a purely biologic factor was strongly exerting itself throughout the whole family line.

The Electrical Shock Treatment of Psychoses. DR. WILLIAM FURST, Morristown, Pa., and DR. JOHN F. STOUFFER.

The use of electricity in the treatment of psychoses is not a recent innovation, since Lovett in 1763 first claimed success in its administration. Huff, in 1853, urged that electrogalvanism be used before any disease is regarded as incurable. Arndt and Albutt, independently using electrogalvanic stimulation, observed improvement in cases of functional mental disease of short duration. In 1900 Leduc first demonstrated that the electrogalvanic current produced loss of consciousness in experimental animals without causing any permanent damage. Rabinovitch, in 1906, described an electrically induced fit in dogs, which she called *epilepsie electrique*. Her work was confirmed by others, but Clark and Wall, in 1934, first called attention to the increased calmness and docility of animals following electric shock. These authors noted an initial fall in blood pressure, which was abolished by section of the vagus nerves. By direct observation through a window in the skull, they found that cerebral stimulation, and not vasoconstriction of the cerebral vessels, was responsible for the convulsions, since stimulation of the proximal end of the cervical sympathetic trunk, while producing vasoconstriction, did not elicit an epileptiform seizure. In 1938 Cerletti and Bini first reported on the use of electrically induced convulsions in treatment of schizophrenia. Since then there have appeared fifteen papers on the results of electric shock in psychotic patients, in all of which the reports were favorable.

The apparatus used for producing electric shocks was essentially similar to that introduced by Cerletti and Bini and utilized an alternating current of 110 volts from a house circuit.

The patients treated in this series were unselected persons with acute and chronic schizophrenia, affective reactions, anxiety neuroses and chronic alcoholism

accompanied by auditory hallucinations and depression, who ranged in age from 14 to 71. The duration of illness varied from two weeks to ten years. The contraindications, preliminary studies and preparation for treatment were essentially the same as those for the metrazol shock treatment.

The patient is placed on a rigid wooden table with the spine maintained in hyperextension. Assistants exert counterpressure against the shoulders, hips and knees, the arms being adducted and flexed across the chest. A cotton mouth gag is inserted between the jaws, which are forcibly held to prevent dislocations. When the resistance is known and the voltage and timer set, the spring switch is pressed. One of three reactions then occurs: (1) a momentary loss of consciousness; (2) a subconvulsive reaction, or (3) a convulsive reaction.

The last-mentioned response is essentially similar to the seizures following the use of metrazol, although the intensity of the convulsion is less and there is no indication of fear, vomiting or muscular pains, commonly observed with metrazol.

Results of Treatment with Electric Shock

	Group *				
	A	B	C	D	Total
Schizophrenia					
Simple	3	3	6	5	17
Paranoid	0	4	2	7	13
Catatonic	1	2	4	10	17
	4 (8.5%)	9 (19%)	12 (25.5%)	22 (47%)	47
Affective reactions					
Manic	3	1	1	1	6
Depressive	6	13	1	7	27
Involutional	16	7	2	3	28
	25 (41%)	21 (34%)	4 (6%)	11 (19%)	61
Alcoholism					
Depression with hallucinations			2	..	2
Psychoneuroses					
Anxiety neurosis	4	..	1	..	5
Total number of cases					115

* In this table, group A includes patients having remission with insight; group B, those having remission without insight; group C, those showing improvement, and group D, those showing no improvement.

Shocks are given three times a week. Improvement is noticeable after three to five treatments, but as a rule it is necessary to "fix" the result with further convulsions, until a maximum of ten is given. If a relapse occurs, a second series is indicated.

Compression fractures of the mid-dorsal portion of the spine occurred in 4 cases in this series (3 per cent) and fracture of the acetabulum in 1 case. In 5 cases complicated by osteoarthritis or previous vertebral fractures, curare was successfully used to prevent further injury. Post-treatment headache was frequent, but was readily controlled with analgesics. The patchy loss of memory which occurred lasted from a few weeks to several months. In 1 case punctate hemorrhages appeared in the conjunctival vessels. The heart suffered from minor arrhythmia. In another case an exacerbation of inactive pulmonary tuberculosis was precipitated. In the affective reaction group an amazing transformation of the symptoms frequently occurred. A severely depressed patient would suddenly become hypomanic, and vice versa. Fortunately, this reversal was of short duration and preceded the return to normal.

Since no deaths due to this treatment have yet been reported, the neuropathologic changes in human subjects are unknown. Cerletti reported that in dogs subjected to multiple shocks of higher voltage than that necessary to induce seizures in man, the cortex showed no changes commonly seen after insulin coma and much less damage than that observed after metrazol shock. In a study of 9 shocked cats, Alpers found minute subarachnoid hemorrhages in 2 animals, but no ganglion or glia cell reaction.

It will be seen from the accompanying table that 75 per cent of the affective reaction group experienced a remission sufficient to permit discharge from the hospital. The average period of hospitalization for this group was forty-five days. Of the patients, 28 per cent were discharged, the hospitalization period averaging three months. During an observation period of seven months, of the patients discharged in remission, 3 with schizophrenia and 1 with manic-depressive psychosis have had recurrences.

The following conclusions are reached:

1. Production of electric shock is a simple, safe and effective method of inducing convulsions for the treatment of psychoses.

2. The complications are less than those occurring during metrazol convulsions.

3. Seventy-five per cent of the patients with affective psychoses and 28 per cent of those with schizophrenia were able to leave the hospital, with an average period of hospitalization of forty-five days for the former and of three months for the latter.

4. Electric shocks should replace other forms of analeptic convulsions in the treatment of psychoses.

DISCUSSION

DR. S. HARVARD KAUFMAN: Although Dr. Furst states that complications due to fracture are less frequent, I believe this still to be open to question. (Statistics of Worcester State Hospital were cited. In a group of 54 consecutive cases of men subjected to a series of metrazol convulsions, with an average of fifteen convulsions per patient, during which the patient was placed on a special restraining hyperextension board, no spinal fracture was demonstrated by repeated roentgenograms. Before these methods of restraint, a 10 per cent incidence was noted.)

Regarding the changes in memory following electric shock therapy, I recall a case in which the patient exhibited the sort of toxic, Korsakoff-like reaction often seen after metrazol.

In considering these results, I wonder why, when there is a more or less controlled method of administering shock, further research in determining the efficacy of the petit mal shock reaction is not carried out. I am aware of the fact that this was tried with metrazol and that, as Cohen of Worcester, Mass., demonstrated, the method was not therapeutically sound.

Freedman at the Norwich State Hospital, Norwich, Conn., with an entirely different electric shock apparatus, is using a minimum voltage and is inducing momentary unconsciousness without convulsions. He is reported to be securing results similar to those obtained with the use of the usual current and convulsion therapy.

DR. ALFRED GORDON: I should like to inquire regarding the follow-up procedure for patients who have received electric shock therapy. How long a period are they kept under observation after treatment in the hospital? There have been reports from various sources regarding the follow-up course of metrazol therapy, and I should appreciate being informed on this point.

Would Dr. Furst be good enough to tell me: (1) How frequently electric shock must be administered, and whether any standard method is being used; (2) what is the criterion for commensurate improvement, and (3) what is the length of the follow-up course?

DR. MATTHEW T. MOORE: Dr. Winkelman and I have conducted experiments with two types of modalities, one being the usual current advocated by Cerletti and Bini and the other the faradic current utilized by Berkwitz. It has been our purpose to combine the present results with those of our studies on metrazol and insulin shock therapy.

With the current used by Cerletti and Bini, the brains of the animals showed minimal changes, consisting of occasional pyknosis of the ganglion cells of the second layer. The animals in this experiment were subjected to greater voltage than that used for human subjects, with a current exposure of one to one and one-half seconds. In a second group of animals receiving an intense current with three times the usual exposure we were unable to find hemorrhages in any part of the brain, and although one of the electrodes was placed posteriorly the brain stem failed to show any evidence of hemorrhage. There was, however, marked congestion of the venous side of the circulation. In those animals receiving the faradic type of current, as used by Berkwitz, we found greater changes, as evidenced by a moderate degree of pyknosis of the ganglion cells, particularly in the frontal areas. Hemorrhage, however, was not encountered.

DR. PAUL SLOANE: There must be some changes in the ganglion cells to account for the marked memory defect, which may last for weeks or months after treatment.

DR. WILLIAM FURST, Norristown, Pa.: Concerning modification of the present method of electric shock treatment, it is my opinion, as it was with metrazol, that subconvulsive doses are of no value. In order to eliminate the various complications of major convulsive seizures, Berkwitz (Faradic Shock in Treatment of Functional Mental Disorders: Treatment by Excitation Followed by Intravenous Use of Barbiturates, ARCH. NEUROL. & PSYCHIAT. **44**:760 [Oct.] 1940) induced subconvulsive shocks with the faradic current in order to produce fear, pain and intense autonomic stimulation in cases of functional psychoses. This was followed by narcosis with pentothal sodium. He reported gratifying results in 73 cases. I do not know how to evaluate this report. In electric shock treatment we noted no improvement until we were able to produce three to five major convulsive seizures. An interesting case was that of a woman aged 68, in whom we were unable to produce a major seizure until she had received a total of twenty-one subconvulsive shocks on seven treatment days. We were unable to observe any improvement until we had produced thereafter ten major seizures.

An interesting change is produced by electric shocks in patients with catatonia. In these patients, with very small multiple shocks, we were able to arouse a catatonic stupor, the result being similar to the relaxation of cerebral inhibition which occurs after the intravenous administration of sodium amytal.

Regarding Dr. Gordon's question of our follow-up studies, I may add that at the Philadelphia General Hospital we are unable to control our cases as carefully as we should like.

As to the frequency of treatment, three electric shocks are usually given weekly for a course of ten treatments.

In the classification of the results of treatment, we use the criteria employed by many workers in evaluating the results of metrazol treatment, namely: (*a*) improvement with psychologic insight; (*b*) improvement without psychologic insight; (*c*) improvement over the admission level, and (*d*) no improvement.

Relapse occurred in 3 patients with schizophrenia and 1 with a manic-depressive psychosis, who returned in a depressed phase.

I should like to comment on the loss of memory which occurs in the patients during this treatment. I am convinced it is transient, but have no explanation for the phenomenon. I have not seen it last longer than two months, and, interestingly, the memory returns in patchy fashion. Patients will comment at first on their impaired memory and then make light of it.

DR. LAUREN H. SMITH: I wish to refer to Dr. Kaufman's remark in regard to the decrease in fractures resulting from the technic employed in handling patients at the Worcester State Hospital during the convulsive episode. Fractures have been reduced to 3 or 5 per cent with electric shock therapy, which is in contrast to the 22 to 30 per cent with metrazol therapy. The number of fractures with metrazol ran considerably higher if those fine line vertebral fractures, which some roentgenologists do not regard as true fractures, were included. With the same technic of management of the patient during the convulsive episode and the same criterion in the roentgenographic diagnosis of fracture, the incidence of fracture with electric shock is definitely reduced.

A Study of the Normal. DR. EARL D. BOND.

Any study of the normal has been hindered by the pressure on well people to tell only so much about themselves as is socially acceptable. In the stress of mental illness not only the patients, but their families, feel the need of telling the truth about themselves as they see it. So in the histories of patients one can find much good evidence of what has caused a temporary or a permanent breakdown.

The growing frankness of modern biography and autobiography is providing case histories of what has happened to persons who have come, not to breakdown, but to great success.

Three illustrations are given, the most interesting of which is the biography of George du Maurier by his grand-daughter, Daphne.

The Electrocardiogram During Electric Shock Treatment of Mental Disorders. DR. SAMUEL BELLET (by invitation), DR. ALFRED KERSHBAUM (by invitation) and DR. WILLIAM FURST.

The electrocardiographic alterations during 100 convulsive treatments produced by electric shock were recorded on 50 patients. Of these, 65 were major and 35 were minor seizures. In this series, the electrocardiographic changes were of minor degree in 98 shock treatments. These included minor arrhythmias: for example, sinus arrhythmias, sinus bradycardia and sinoauricular heart block, in 35 instances; auriculoventricular nodal rhythm, in 2 cases; shifting pacemaker, in 2 cases, and auricular extrasystoles, in 1 case. Slight changes in the T and S-T segments in lead II were observed in 18 instances.

In only 2 instances were more serious results encountered—in older patients, aged 47 and 54, respectively, and then under unusual circumstances. The first consisted of the production of inverted T waves in leads I and II following a delayed convulsive seizure, and the second, a serious type of arrhythmia following electric shock after the use of curare.

DISCUSSION

DR. ALFRED GORDON: How soon after shock treatment did Dr. Bellet observe the series of electrocardiographic changes? On reexamination, after the so-called recovery from the electric shock therapy, did these changes remain or disappear?

DR. ROBERT A. MATTHEWS: The fact that Dr. Bellet found changes in the electrocardiogram of at least 1 patient to whom curare had been administered brings up the question, raised by Dr. Kaufman, in his discussion on the paper by Dr. Furst and Dr. Stouffer, as to the need for employment of subconvulsive doses or a subconvulsive technic in certain cases in which it is inadvisable to produce a convulsion. There are a number of cases in which the production of convulsive seizures is contraindicated, and if by use of curare the life of that patient is endangered, not only through the action on the central nervous system but also

through damage to the heart, a technic which will allow some of the results of subconvulsive doses should be worked out.

I recall the case of a 73 year old woman who had had four previous depressions and who, when admitted to the Pennsylvania Hospital, was in a state of agitated depression, with a marked delusional trend of four months' duration. Six electric shock treatments were administered without a single convulsion, and she made a prompt and complete recovery after the third nonconvulsive treatment. That does not coincide with the statement of Dr. Furst that he obtained no satisfactory results in patients who did not reach the convulsive dose. However, the patient in question had a very high convulsive threshold, which may have had a bearing on the problem. I wonder if an effort was made at the Philadelphia General Hospital to carry a patient through five to eight treatments without convulsions.

In the case of certain schizophrenic patients receiving insulin therapy a few electric shock treatments (previously metrazol was used) are given if the patient does not show a satisfactory degree of improvement with the insulin alone.

In view of Dr. Bellet's results in the cases in which insulin was used, it would seem like adding insult to injury to expect the heart to withstand the hazards of insulin coma and electric shock.

DR. SAMUEL COHEN: What are Dr. Bellet's observations on epileptic patients after induction of seizures? Have any postconvulsive cardiac changes of a serious nature been reported?

DR. ALFRED GORDON: How soon after therapy, Dr. Bellet, do you take an electrocardiogram?

DR. SAMUEL BELLET: In reply to Dr. Gordon's question concerning the follow-up study of patients receiving electric shock: We have followed every patient who showed definite electrocardiographic alterations that persisted after the convulsive seizure. The only patient who showed evidence of cardiac damage after electric shock therapy was followed for approximately two and one-half months. During this period there was a definite tendency toward a return to normal.

One cannot make an electrocardiographic study during a convulsive seizure because of movement of the galvanometer string. Records are taken immediately after the convulsive attack and are continued for approximately eight minutes. If any changes persist after this period, a longer period of recording is required.

Except for our experience in 1 case, I know of no other instances in which convulsions occurred after electric shock. Several instances of delayed convulsive seizures following metrazol therapy are recorded in the literature. The electrocardiographic change in these cases is of a type similar to that which we noted after electric shock, namely, inversion of the T waves.

We have made no electrocardiographic studies during epileptic seizures.

Electroencephalographic Studies on Patients Receiving Electric Shock Treatment. DR. JOSEPH HUGHES, DR. ROBERT WIGTON (by invitation) and DR. FREDERICK JARDON (by invitation).

Records were obtained before, during and at various intervals after each of a series of electric shock treatments in 16 subjects.

Rhythm During the Convulsion.—During the latent period there appear large spiked waves of high frequency, which increase in amplitude and persist during the tonic phase. As the clonic phase develops the spiked waves become grouped into bursts, and large slow potential alterations occur which are synchronous with the clonic jerks.

Postconvulsive Rhythm.—After the last jerk, the record is unusually quiet and remains so for one to two minutes. During the second minute there appear groups of large (200 to 400 microvolts) slow (2 per second) waves. At the third or

fourth minute these large slow waves are continuous and more irregular in contour. They then become more random and rapid and smaller, until they are replaced by the normal rhythm at the end of an hour.

Subconvulsive Reactions.—In the type of subconvulsive reaction characterized by only momentary loss of consciousness, there is striking absence of any large cortical potentials. During a second type of reaction the patient remains unconscious and apneic for a period corresponding to a convulsion, but no convulsive movements occur. The electroencephalographic record during this period is similar to that during a convulsion, even to the occurrence of a gradually decreasing slow wave rhythm, which seems to correspond to the clonic phase, although the patient shows no movements.

After successive convulsions during a series of treatments, the abnormal waves persist for longer periods, so that after six or seven treatments they may be observed for several days, and may not entirely disappear for two to three weeks after the last treatment. In some patients the tendency to development of these potentials was much greater than in others.

Although the origin and significance of these unusual potentials are not known, several observations relative to their nature were noted: (1) They tend to be bilaterally synchronous and equal in size; (2) they are largest in the prefrontal areas, being smaller in more posterior placed leads, and (3) they tend to be noticeably diminished if the patient is apprehensive or attentive (as after a start or during attention to a thought problem).

There does not seem to be any direct correlation between the development of these potentials and either the disappearance of psychotic symptoms or the occurrence of loss of memory and confusion, as seen in these patients.

DISCUSSION

DR. ELI MARCOVITZ: What is the longest period after treatment before the electroencephalographic studies returned to normal? Were these abnormal waves correlated with disturbances in memory?

DR. WILLIAM FURST, Norristown, Pa.: I should like to know whether the authors could detect any difference in the tracings of manic and those of depressive patients following electric shocks.

In the hypomania frequently induced in depressive patients, following the conclusion of electrical treatments, is there a significant change in the electroencephalogram?

DR. PAUL SLOANE: Has it been noted that greater changes occur in older people, particularly those with arteriosclerosis?

DR. R. S. WIGTON: In reply to Dr. Marcovitz, the longest period after treatment before the electroencephalogram returned to normal was three or four weeks. It is difficult to determine this period exactly, as the potentials decrease considerably throughout the first and second week, presenting only a slight deviation from the normal in the third week.

There did not seem to be any direct correlation between loss of memory and the development of these potentials other than the fact that both abnormalities gradually disappeared during approximately the same interval.

Some patients with a large amount of abnormal activity showed slight loss of memory, and vice versa.

There was no apparent difference in the records of the manic or depressed patients or in the records of those who recovered and those who did not.

In reply to Dr. Sloane, the younger patients seemed to show more abnormal waves, whereas the older ones were apt to manifest the most pronounced memory loss, an observation which further illustrates the lack of coordination between memory loss and the electroencephalographic changes.

PHILADELPHIA NEUROLOGICAL SOCIETY

BERNARD J. ALPERS, M.D., *Presiding*

Regular Meeting, April 25, 1941

Recrudescence of Encephalitis. DR. ALFRED GORDON.

It is fairly well established that the virus of encephalitis lethargica may invade any area of the central nervous system. As to the so-called sequelae, the literature shows a multiplicity of phenomena. The nervous system, the special sense organs, the motor system, the vegetative nervous system, the psychic functions, all may show morbid alterations. Some of these various manifestations are rare, or very rare, while others are common. Hyperkinetic phenomena are the most frequent.

Since in some cases the postencephalitic sequelae are chronologically not far removed from the original malady and since usually, when they do occur, they remain fixed, it seems logical to conclude that the pathologic substratum, which is directly responsible, is fixed and shows no tendency to extension and further involvement. On the other hand, there are cases in which the preexisting symptoms are aggravated and new manifestations appear.

Such observations, of course, can only signify progressive and extensive development of the original lesions, due in all probability to persistence of the encephalitic virus in the nerve tissue. The clinical histories in many such cases indicate that the virus may remain active in the nerve tissue for a considerable time and that it is capable of causing new anatomic lesions and extensions of preexisting ones. They also indicate that there is no certainty as to whether the virus is ever completely eliminated and, if elimination is possible, within what period it may be accomplished. It is uncertain, also, should the virus be eliminated, whether the lesions can regress, and to what extent and with how much consequent amelioration of the clinical manifestations. Present therapeutic resources do not include any method of neutralizing the virus in order to obtain regression of the anatomic lesions and, consequently, modification in the course of the syndrome.

The postencephalitic manifestations should be considered not merely as sequelae but as forms of a genuine chronic involvement in the presence of a virus which is still active, and the apparent subsidence of an encephalitic invasion does not necessarily indicate that the process is finished, for the virus may exist in a latent state, even for many years, during which time the clinical manifestations will remain unaltered and fixed. Recrudescences may develop, not only after the acute state but also many years later, and new phenomena may appear in the domain of any segment of the central nervous system.

The succession of pathologic manifestations in the same person at intervals of years demonstrates that the so-called sequelae are not of evolutional character, but are late and definite reactivations of the original infectious process, especially characteristic of lethargic encephalitis. The observations have a considerable and serious bearing on the prognosis in this grave disease. They prove that it would be erroneous to assume a final position as to the course of lethargic encephalitis even after the parkinsonian syndrome becomes definite, and the prognosis should therefore be made with great reservation.

In a typical case of parkinsonian syndrome, subsequent to an attack of lethargic encephalitis fifteen years earlier, the patient has manifested at different periods, with intervals of years between each, the following phenomena, namely: oculogyric crises, six years after the onset of encephalitis; attacks of rigidity and immobility of the tongue, five years later still, and attacks of uncontrollable closure of the eyelids, with hypertonicity of the orbicularis palpebrarum muscles, about three months ago.

In another case the following course of events was observed during a period of seven years: At first there was a typical picture of encephalitis lethargica.

Shortly after the acute period there developed an unusual speech disorder, which still persists, as well as myoclonia and tremor of the left hand. The next abnormal symptom (appearing four years later) was a paretic state of the right arm, which progressively increased. Next in the chronologic order (in the fifth year) was the extensor plantar reflex on the right side, and finally progressive spasmodic torticollis became established. The speech disorder, with particular disturbance of the function of the tongue in the act of speaking, may be the result of nuclear involvement in the medulla, or rather of an interruption in the structural connection of the striatum with the important bulbar segments of the central nervous system.

In a third case, a girl of 10 years had a typical attack of lethargic encephalitis at the age of 6, which was followed by mild right hemiplegia and choreic movements on the opposite side. After considerable improvement, which permitted her to resume school work and even dancing, three years later, after a mild cold, the former motor symptoms returned with greater intensity, and new symptoms, referable to involvement of several cranial nerves, made their appearance.

In these 3 examples we observe several encephalitic sequelae, developing with very long intervals between each; they demonstrate the existence of latent or silent periods of years after the acute infection. Therefore, the assurance of a final, fixed stage in the disease is not possible.

Effective Therapy in the Syndrome of Crocodile Tears. Dr. F. H. Leavitt and Dr. B. H. Gottesfeld.

On the basis of the work of Fowler and Ford in this country and of Purves-Stewart abroad, an effective form of therapy has been applied to the syndrome of crocodile tears. In a verified case of Bell's palsy, the sequel of unilateral epiphora induced by eating should focus the clinician's attention on this syndrome.

The regeneration of visceral efferent fibers from the facial nerve to the greater superficial petrosal nerve through the sphenopalatine ganglion and then by way of the second division of the fifth nerve, via the zygomatic nerve, to the first division of the fifth nerve and then to the lacrimal gland offers a clue to the satisfactory interruption of the regenerating fibers.

The patient in the case reported presented a history of facial paralysis, which generally follows refrigeration or exposure. In the course of time and with the usual modes of therapy, there were progressive regeneration of the nerve fibers and recovery of parts of the facial musculature. Several months later the patient noted the sudden appearance of epiphora on chewing or eating. All attempts at medication failed to alleviate this symptom. The syndrome may last for years.

In such cases, in which there is persistent epiphora, it is wise to anesthetize the posterior naris of the affected side with a 2 per cent solution of cocaine hydrochloride. The epiphora will disappear temporarily, owing to anesthetization of the sphenopalatine ganglion. Injection into the sphenopalatine ganglion of absolute alcohol by way of the posterior palatine foramen should be the second step. The patient will report complete disappearance of epiphora.

Follow-up examination in the present case revealed a normal cornea and partial paralysis of the soft palate on the same side, which did not disable the patient, and the complete absence of associated epiphora with eating. In view of the successful result, it is recommended that injection of absolute alcohol into the sphenopalatine ganglion be performed in treatment of the syndrome of crocodile tears.

DISCUSSION

Dr. F. H. Lewy: I did not quite understand the mechanism involved. If cocainization was effective, it means that sensory fibers were anesthetized. These fibers go to the second division of the fifth nerve. Did I understand that correctly?

Dr. R. A. Groff: I think that I can answer, in part, the question which Dr. Lewy has raised. The usual procedure in determining whether a patient has

pain originating in the sphenopalatine ganglion is to cocainize the posterior portion of the nares. This simple procedure is effective. Such a test is always performed before alcohol injections are attempted. The presentation of Dr. Leavitt and Dr. Gottesfeld bears out some of the facts that Dr. Lewy and I had emphasized in connection with the autonomic fibers in the first, second and third divisions of the fifth cranial nerve. Both Dr. Gottesfeld and we agree that there are autonomic fibers within the first division of the fifth nerve. In light of the explanation that has been made for the syndrome of crocodile tears, it occurred to me that injection of the sphenopalatine ganglion might be the answer to relief from the ticlike associated movements of the Marcus-Gunn phenomena.

DR. F. H. LEAVITT: When this man first came into the clinic, the contraction of the orbicularis muscle made me think of the Marcus-Gunn phenomenon. I do not think this condition is such a rare one, since recently a patient was seen with facial palsy, presenting the same condition as that in the present case.

DR. B. H. GOTTESFELD: In reply to Dr. Lewy's question, I should like to point out that the greater superficial petrosal nerve fibers are transmitted by way of the hiatus fallopii and run in a small groove on the anterior surface of the petrous bone, beneath the dura mater and the gasserian ganglion, to the sphenopalatine ganglion. The secondary fibers are then transmitted by the superior maxillary branch of the trigeminal nerve. From the second division the fibers are transmitted by the lacrimal division of the fifth nerve to the lacrimal gland. By cocainization we aim to remove the influence of this group of fibers.

Many textbooks of physiology explain the supply of the lacrimal gland by stating that the visceral efferent fibers are transmitted through the greater superficial petrosal nerve. Consequently, if one blocks the sphenopalatine ganglion, a dry eye should develop on the affected side. In this patient such a phenomenon did not appear. I believe Dr. Groff mentioned the fact that some secretomotor fibers may be transmitted through the fifth nerve and in that way make up a secondary secretory component of the lacrimal gland.

Effect of Vitamin E on Progressive Muscular Dystrophy and Amyotrophic Lateral Sclerosis. DR. B. J. ALPERS, DR. H. S. GASKILL, DR. A. CANTAROW and DR. H. E. YASKIN.

Six patients with progressive muscular dystrophy and 6 with amyotrophic lateral sclerosis were treated with alpha tocopherol and vitamin B complex for periods of six to twenty-three months. Two of the 6 patients with amyotrophic lateral sclerosis have died during the course of treatment, and the 4 remaining patients have not been benefited by the therapy.

No alteration was found in the neurologic status of 5 of the 6 patients with progressive muscular dystrophy, although 2 of these patients reported marked subjective improvement. The sixth patient has become worse despite treatment. The amounts of creatine and creatinine excreted in the urine were determined before and at various times during therapy. Treatment was ineffectual in altering the abnormal creatinuria and creatininuria.

d,l Alpha Tocopherol Acetate (Synthetic Vitamin E) in Treatment of Various Neuromuscular Disturbances. DR. G. A. SCHWARZ, DR. G. D. GAMMON and DR. R. L. MASLAND.

Vitamin E in the form of d,l alpha tocopherol acetate was administered in 18 cases of various neuromuscular disorders. In the group studied, there were 8 cases of progressive pseudohypertrophic muscular dystrophy, 4 cases of the adult form of progressive muscular dystrophy, 1 case in which the differential diagnosis of dystrophy or amyotonia congenita was not certain, 1 case of progressive spinal muscular atrophy, 2 cases of amyotrophic lateral sclerosis, 1 case of lateral sclerosis and 1 case of posterolateral sclerosis, of undetermined origin.

All of the patients took the alpha tocopherol by mouth. The daily dose was 50 mg. Fifteen of the patients took 50 mg. per day for four months or longer. Eleven patients also took whole wheat germ cereal in amounts of 1 to 3 ounces (28 to 85 Gm.) daily. Sixteen patients also took brewers' yeast tablets in doses of 15 grains (0.975 Gm.) daily.

By repeated neurologic examinations, we were not able to detect improvement in any of the cases. In 1 case each of amyotrophic lateral sclerosis, progressive muscular atrophy and muscular dystrophy of the adult form we observed definite progression of the signs and symptoms throughout the period of treatment. Subjectively, in 5 cases of muscular dystrophy the patients reported that they felt generally stronger and less fatigable. Objectively, as noted by friends or relatives, 4 patients with dystrophy were reported at different times to show minor improvement.

We conclude that the doses and duration of treatment used in our cases have not yielded encouraging results with respect to the value of vitamin E in treatment of certain neuromuscular diseases in man.

DISCUSSION ON PAPERS ON VITAMIN E BY DR. ALPERS AND DR. SCHWARZ AND ASSOCIATES

DR. G. D. GAMMON: As Dr. Schwarz reported here, the results in this small group of cases were distinctly discouraging from the point of view of clinical improvement. In treating patients with dystrophy the difficulty, of course, is in evaluating the progress of the disease. Unfortunately, the yardstick of creatinuria, which Dr. Alpers and Dr. Gaskill first felt might prove useful, has on subsequent study failed to provide any adequate measure of the progress of the disease in relation to clinical tests.

If this disease cannot be cured by vitamin E, but only arrested, one must be able to say that the downhill course is retarded or stopped. This requires observation over a considerable period. Since we have treated many patients with these disorders, particularly the dystrophies, for several years with various therapeutic agents, including liver extract, yeast, vitamin E and vitamin C, we may perhaps claim that we are familiar enough with such patients to be able to judge their clinical course. Under these circumstances, we feel rather definitely that our results with vitamin E in the doses used have not been particularly encouraging.

DR. H. E. YASKIN: I have had the opportunity to follow the 6 patients with amyotrophic lateral sclerosis included in the series reported by Dr. Gaskill. They were all given daily a minimum of 125 mg. of alpha tocopherol by mouth and at least 100 mg. by muscular injection. All were placed on a high vitamin E diet, which included corn in season, green peas, cereals, nuts, fat beef, rice and bananas. Four of these patients received approximately one year's treatment under this regimen. Two of these patients, who had been ill longer than two years when the treatment was started, have died. In 1 of these 4 patients bulbar symptoms developed under treatment. The remaining 2 show slight progression of signs. Of the 6 patients, 2 have received treatment for a period of six months, and their disease has progressed while they have been under observation. From these results one gets a dubious impression of the value of vitamin E in this condition. However, the 2 patients who died had a chronic advanced form of the disease. Some workers might criticize Dr. Schwarz's series of cases on the basis that the patients have not received a sufficient amount of vitamin E for a fair therapeutic trial. I believe it would be better to overtreat such patients with vitamin E, in order to meet this criticism.

DR. G. A. SCHWARZ: I think I answered the criticism which might be directed toward this treatment, namely, that the patients have been undertreated with a vitamin E regimen. Dr. Wechsler now considers adequate a therapeutic regimen of approximately 250 mg. of alpha tocopherol given by mouth and 200 mg. injected intramuscularly, 1 ounce (29.5 cc.) of wheat germ oil with a high vitamin E

diet and, in some cases, bile salts. As to whether lack of vitamin E causes neuromuscular disturbances, it has been shown experimentally that alpha tocopherol can prevent and alleviate the syndrome; so I feel that criticism of the therapy should not be pointed in that direction. It might be well to standardize the dose for patients treated for such disorders, so that we might better evaluate results in years to come.

DR. B. J. ALPERS: I should like to say a few words with regard to my experience with these dystrophies. First, it seems to me that this is a deflationary period with regard to the treatment of such dystrophies with vitamin E, and this after very enthusiastic reports, notably those of Stone. One is bound to meet disappointments in experience with vitamin E therapy, but one's attitude should not be as deflationary as it seems to be. I do not think one can say that vitamin E has no value in the treatment of muscular dystrophies; furthermore, one should distinguish between muscular dystrophies and amyotrophic lateral sclerosis in evaluating the treatment. There is good evidence that vitamin E produces muscle tonus. Then there is the question whether nutritional dystrophy is the same as muscular dystrophy. I think that question is still unanswered, and will remain so for a long time, in view of the conflicting reports.

My associates and I have had only a little evidence of improvement with the use of vitamin E. We have been able to walk patients upstairs, farther than they could ever walk before treatment. Most of the evidence of improvement has been subjective, and as such is fallible. I did not hear Dr. Schwarz say anything about this phase of the treatment, but most of our patients have attained a sort of euphoria under treatment with vitamin E; they have a sense of well-being as long as they are taking the vitamin, and I believe it is not simply because they have a chronic disease and are getting something new. I think they get a lift with vitamin E over a fairly long period. I wish Dr. Gaskill had given data regarding some of the patients who improved. Maybe he will state just what patients improved. Two of our patients can do more than they could before treatment. At least a few of our patients with muscular dystrophy have shown slight improvement, albeit I recognize the fact that such improvement may occur with other types of treatment. One is being premature if one says there is no response to vitamin E therapy.

DR. H. S. GASKILL: The 2 patients who reported subjective improvement show little objective evidence of this other than a moderate gain in weight. However, two friends of 1 of these patients said that they had noticed a definite change in him since he had been under treatment. He was now able to walk much farther without resting, could walk uphill and was able to throw a ball more easily.

The second patient, at the time treatment was begun, was unable to hold a steady position, since he tired so quickly. During the past winter, however, he worked as a laborer for a number of months, and more recently he held a clerical position. These evidences of improvement, meager as they are, are difficult to disregard completely. It is still too early to make a definite statement concerning the value of this therapy.

DR. S. F. GILPIN JR.: The dystrophies, I think, undergo spontaneous remissions. The remarkable temporary improvement often possible from suggestion alone should, I think, be emphasized in this consideration of results. Dr. Lewy procured some vitamin B_6, which was tried at the Philadelphia General Hospital. We did not have much of the substance to work with. One patient with encephalitic parkinsonism was, and is, chair fast. After six doses of pyridoxine hydrochloride he took several steps alone and stood by himself. We had only six doses to give him, which was too little to obtain any results; yet there was remarkable objective improvement.

I think it is also worth emphasizing that every one, as a result of enthusiasm, is apt to report good results without waiting long enough. As an example, I think of the case of a man who has progressive spinal muscular atrophy. While he

was taking brewers' yeast, and also alpha tocopherol, I have seen him make objective improvement, with increase of muscle strength and improvement in gait and the distance he could walk, and this has been noted by others than myself. First he improved, and then he failed, although he was taking the same amount of both these preparations. If we had not waited, or if some one had become overenthusiastic, we might have made premature claims.

Solitary Tumor of the Sciatic Nerve. DR. J. C. YASKIN, DR. J. T. NICHOLSON and DR. R. A. GROFF.

Multiple tumors of the von Recklinghausen type are relatively common in the spinal nerves, as is also traumatic neuroma. Solitary tumor is common in spinal nerve roots, but is rare in the spinal nerves themselves. Small groups of cases have been reported by Lewis and Hart (*Ann. Surg.* **92**:961, 1930), Sarroste (*Rev. de chir., Paris* **53**:608 [Oct.] 1934), Stout (*Am. J. Cancer* **25**:1, 1935), Cutler and Gross (Neurofibroma and Neurofibrosarcoma of Peripheral Nerves Unassociated with Recklinghausen's Disease: Report of Twenty-Five Cases, *Arch. Surg.* **33**:733 [Nov.] 1936) and by others. The diagnosis of solitary tumor of the extremities is usually difficult and, as a rule, is established only by operation.

The following case, which is the only one we have encountered, is deemed worthy of reporting.

REPORT OF A CASE

History.—R. R., a 29 year old married woman, with irrelevant family and past medical histories, complained of pain in the back of the left thigh for seven and a half years. The pain was most marked in the back of the thigh and down the entire leg, but it was also present in the lower lumbar region. The patient stated that the pain was fairly constant day and night and that she had had but few remissions, of short duration, in the last seven years.

There was a point of exquisite tenderness in the course of the left sciatic nerve just below the gluteal fold. This point of tenderness was constant on numerous examinations, and there was no tenderness in any other part of the nerve. Lasègue's sign was absent bilaterally. Careful palpation failed to show any masses in the region of the point of tenderness. There was slight diminution of the left knee jerk.

Routine laboratory studies revealed nothing abnormal. A spinal tap gave normal hydrodynamic readings, and the spinal fluid was normal.

The diagnosis of a tumor along the course of the sciatic nerve was made, and on Nov. 5, 1940 an exploratory operation was performed by Dr. J. T. Nicholson and Dr. R. A. Groff, with the patient under anesthesia induced with nitrogen monoxide, oxygen and ether.

Operative Procedure.—The posterior cutaneous branch of the sciatic nerve was identified and freed from the biceps sheath and the lower portion of the gluteus maximus muscle. A rounded mass, approximately 5.5 cm. in length, was exposed. This was observed to be continuous with the sciatic nerve below and firmly attached throughout its length. At the upper portion the fibers of the sciatic nerve were firmly adherent to it. With a suture through the lower pole of the tumor, the mass was retracted proximally, and a plane of cleavage was found between it and the sciatic nerve fibers. As the dissection was continued upward to the proximal end of the tumor, a nerve bundle was found to lead directly into it. This was ligated and cut through. The lower pole of the tumor was observed to extend into a nerve bundle which gave every indication of being the same bundle that was divided at the upper pole. This lower portion of the nerve bundle was likewise tied and divided. The nerve sheath was then allowed to fall back over the exposed sciatic nerve, and the wound was closed.

Pathologic Study.—The tumor measured 4.4 cm. in one diameter and 2.5 cm. in the other. It was more or less spherical and appeared to be encapsulated.

Microscopic examination revealed a loose neurofibroma, with edema, very large blood vessels, hemorrhage and areas of hyalin and bone.

Course.—The patient made an uneventful recovery and was discharged in two weeks, without neurologic signs. She has remained free from symptoms since the operation.

Comment.—The diagnosis in this case was made on the basis of (*a*) continuous pain in the course of the sciatic nerve for seven and a half years; (*b*) constant exquisite localized tenderness in the course of the sciatic nerve, and (*c*) exclusion of other possible etiologic factors.

While tumor is a rare cause of sciatic pain, it is worth remembering that such lesions do occur and that the proper diagnosis and treatment are extremely gratifying, especially to the patient.

DISCUSSION

DR. J. T. NICHOLSON: In the literature lesions of the sciatic nerve have been discussed, but have not attracted much attention. Without alluding directly to tumor, there have been references to adhesions about the sciatic nerve, with the local point of tenderness in the region of the gluteal fold, as was significant in the present case. In 1913 10 cases were reported by Dr. William J. Taylor, of Philadelphia, and again in 1922 these cases were reviewed. They were of persons who had been exposed to changes in temperature or to trauma. Singularly, their occupation was that of chauffeur or fireman. Operation revealed a definite band of adhesions about the sciatic nerve. The first reference to such adhesions of the sciatic nerve was made by Ranson, in 1898. In 1939 Dr. George Wagoner (*Surgery* **5**:609 [April] 1939) reviewed 24 cases. He pointed out that the significant findings were absence of the ankle jerk, atrophy and hyperesthesia.

Our first case reported was that of a man who had had sciatic pain for four years. He had weakness of dorsiflexion of the foot and absence of ankle jerk. Exploration of the sciatic nerve was made, but not particularly in anticipation of finding a tumor. Other studies had yielded no results. Interesting enough, after the upper part of the sciatic nerve was exposed by detaching the gluteus maximus muscle from the greater trochanter and retracting the muscle upward, a stricture of such extent was encountered beneath the pyriformis muscle that it was impossible to pass the examining finger along the nerve through the sciatic notch into the pelvis. After reflecting the pyriformis, a spindle-shaped band of adhesions, ¼ inch (0.6 cm.) in thickness and 2 inches (5 cm.) long, was exposed. This band was contracted around the sciatic nerve. The adhesions were dissected free; they were closely in contact with the sheath and could not be dissected on the inner side for fear of dividing the branches of the nerve going to the adductor muscle. This man improved rapidly after operation.

With the recent enthusiasm expressed over lesions of the nucleus pulposus, it is apparent that many sciatic lesions are misinterpreted.

DR. R. A. GROFF: The tumor was interesting in that it was on the posterior surface of the sciatic nerve. It was attached to the nerve by four or five nerve filaments at the upper pole, and these filaments could be seen emerging from the tumor at its lower pole. These filaments were sacrificed, and the tumor dissected out clean, without disturbing the sciatic nerve.

Spinal Epidural Hemorrhage. DR. J. C. YASKIN and DR. R. A. GROFF.

Spinal epidural hemorrhage occurs most commonly after severe trauma to the spine. Usually the vertebrae are severely injured, the subarachnoid space contains blood and the spinal cord gives immediate evidence of compression. Patients with this type of injury usually die, and the epidural bleeding is an inconspicuous part of the total clinical picture.

The following case is reported because the trauma was slight, the symptoms developed slowly several days after the original trauma and the compression of the spinal cord was due entirely to an epidural hemorrhage in the upper thoracic portion of the spine.

REPORT OF A CASE

C. R., an unmarried woman aged 21, with irrelevant family and past medical histories, was admitted to the service of Dr. J. C. Yaskin, at the Graduate Hospital, on Nov. 23, 1940. She had complete paralysis of both lower limbs and retention of urine.

Three weeks prior to admission the patient tripped and fell down several steps and landed on the lower part of her spine. She experienced no immediate ill effects and continued working for the next thirteen days.

Two weeks after the injury she experienced for the first time an attack of pain in the middle of the back, at the level of the angle of the scapula. A few days before this she is said to have had a sore throat; however, there was no other evidence of infection.

A second attack of mid-dorsal pain occurred the following day. The pain radiated to the front of the chest. This was repeated the next day, and at night the pain was associated with numbness of the toes and feet. Within two hours of this complaint she became completely paralyzed in both legs. She had to be catheterized. The day after the paralysis of the legs occurred the pain in the back disappeared.

She was admitted to a hospital on November 17, twenty-four hours after the paralysis had set in, or two weeks after the fall. A roentgenogram of the vertebral column was normal. A lumbar puncture revealed normal fluid and physiologic pressure values. She was transferred to the Graduate Hospital on November 24.

Examination on Admission.—The patient was rather obese. She was intelligent, cooperative and lucid. The temperature was 98 F., the pulse rate 104 and the respiratory rate 22.

The cranial nerves and upper extremities showed no neurologic abnormalities except for occasional nystagmoid jerks on extreme lateral deviation of the eyes. The abdominal muscles were paralyzed. The intercostal muscles, however, showed good function. The patient could not sit up. The abdominal reflexes were absent. The rectal sphincter was atonic and insensitive. Both lower extremities were paralyzed and flaccid. The patellar and achilles reflexes were absent, and plantar stimulation produced little, if any, response.

Sensation was markedly disturbed. Pain sense was absent up to the seventh dorsal segment. Heat and cold sensations were lost in a corresponding area about 2 inches (5 cm.) below the pain level. Touch sense was diminished, but not lost, in the area where pain and temperature senses were absent. Position and vibration sensations were completely abolished in the lower extremities, over the sacrum and probably over most of the vertebral column. There was no evidence of meningeal irritation.

Course in Hospital.—The day after the patient's admission the temperature rose to 102.5 F. and the pulse rate to 120. On the third day she began to vomit, and by evening went into shock. The temperature was 104.5 F. by axilla, the pulse rate 160 and the respiratory rate 30. As the night progressed her vomiting became fecal, and diarrhea set in. The leukocyte count was 26,000. A surgical condition of the abdomen was considered, but a surgical consultant did not find evidence to support this view.

On the fourth day the patient appeared moderately toxic, and decubitus developed on the heels and back. Examination revealed no source of infection. The neurologic signs showed progression in that the level of anesthesia rose to the fourth thoracic segment and was more complete than previously.

During the next two days the patient continued to show a septic temperature and had four chills. She had a constant watery diarrhea. Microscopic examination of the stools showed nothing except a few pus cells. Results of examination of the urine remained negative. A sigmoidoscopic study by Dr. Bockus revealed a mucous membrane suggestive of a neoplastic process with necrosis. Biopsy of a specimen did not reveal tumor.

A lumbar puncture on the fifth day of her stay in the hospital disclosed clear fluid, and the Queckenstedt test gave questionable evidence of a partial block. Spinal puncture, repeated on the tenth day, showed faintly xanthochromic fluid, and dynamic tests revealed complete block. Culture of the spinal fluid yielded organisms which were considered contaminants. A blood culture was sterile.

Moderate anemia had developed in that the red cell count fell from 5,040,000 to 3,850,000, with 57 per cent hemoglobin. The urine remained normal. The Wassermann reactions of the blood and spinal fluid were negative. The neurologic picture remained the same, the sensory level remaining at about the fourth thoracic segment.

On the seventh day after admission, December 1, it was decided to explore the upper thoracic portion of the spine. This decision was based on the following facts: (*a*) The patient was doing poorly; (*b*) a subarachnoid block was demonstrated by Queckenstedt examination, and (*c*) a stationary sensory level was obtained, which served as a site for operative intervention. The provisional, or preoperative, consideration was an extradural abscess or a primary or metastatic tumor.

Operation (Dr. R. A. Groff).—The first, second and third spinous processes and laminas were removed. Beneath the second lamina and occupying the entire epidural space, more on the left than on the right, was a hematoma, which measured about 4 cm. in length and 1.5 to 2 cm. in thickness. It was definitely encapsulated and was well organized toward the dura, to which it was firmly attached. The hematoma was completely removed. The dura was opened, and the spinal cord showed definite evidence of compression, with decrease in vasculature and suspicious softening. The wound was closed.

Postoperative Course and Present Condition (April 1941).—In the succeeding few weeks after operation there was a return of sensation in the lower limbs and lower portions of the trunk. Flaccid paralysis was replaced by the spastic type, increased reflexes, bilateral ankle clonus and Babinski sign and flexor spasms. The legs remained useless. The bladder retained urine, and an indwelling catheter was employed. The bowels required daily enemas for evacuation. The patient had several episodes of fever, undoubtedly due to recurrent cystopyelitis.

Comment.—Spinal epidural hemorrhage is one of the rare causes of compression of the cord. In this patient it occurred several days after a minor trauma. The mechanism of the spinal epidural bleeding is not clear. Undoubtedly earlier recognition and surgical intervention would have saved this patient from invalidism.

DISCUSSION

Dr. R. A. Groff: The case just presented is very similar to that reported to me by Dr. Reed Harrow, of Salt Lake City. He had under his care a young woman with the history that while reaching for a ball on top of a Christmas tree, she experienced a sudden pain in the legs, which was subsequently replaced by paraplegia. The diagnosis in this case rested between hematomyelia and traumatic transverse myelitis and was made by studies with iodized poppyseed oil. At operation a hematogenous tumor, which was entirely extradural, was removed. Dr. Harrow sent a section of this so-called tumor to Dr. Alpers, who made the diagnosis of hematoma. This is the second case of which I know personally. These 2 cases show that the trauma is mild and that the picture cannot be differentiated from hematomyelia with any degree of assurance.

DR. B. J. ALPERS: This case was interesting, and a rare instance of compression of the cord. Was the bleeding arterial or venous?

DR. F. H. LEWY: I wonder about the late appearance of clinical signs. If the results of the first examination can be trusted, the patient had no block in the beginning, and two weeks later a block was present. Is that not similar to the condition called chronic subdural hematoma?

DR. J. C. YASKIN: I stated in the presentation that the modus operandi of the venous bleeding is not clear. The symptoms developed two weeks after injury. Were there no bridging symptoms? This girl presented no other condition which would explain the epidural hemorrhage. There was no evidence of any hemorrhagic disease or any history of trauma.

DR. R. A. GROFF: With respect to Dr. Lewy's question: In this particular case the lesion was exactly like a hematoma, being encapsulated. Under these circumstances it is obvious that periodic bleeding can take place. The slowness of the bleeding was responsible for the delayed clinical picture. I believe that in this case the source of the bleeding was from the meningorachidian veins.

Book Reviews

Foundations of Neuropsychiatry. By Stanley Cobb. Price, $2.50. Pp. 231. Baltimore: Williams & Wilkins Company, 1941.

This book is the second revised and enlarged edition of the author's "A Preface to Nervous Disease." To the former edition have been added some of the more recent neurologic advances and a chapter on psychopathology. However, it is still far from a bulky volume, running only to 225 pages, with excellent references at the end of each chapter, and it is written in a delightfully personalized, succinct manner.

Dr. Cobb lays a condensed anatomic framework for the concept of functional integration, which is his main thesis. He continually emphasizes the unity of structure and function and summarizes this in his excellent chapter on "Consciousness and the Mind-Body Problem."

While this book will not replace the standard texts of neurology and psychiatry, it makes a worthy attempt to bring these fields closer together. In this respect the neurologic aspects far outweigh the psychiatric. Although a chapter on psychopathology has been added, it is not too well coordinated with the rest of the material, in that integrated neurologic functioning is only one aspect of total personality functioning and therefore falls short of explaining "the stuff out of which psychopathology is made."

This book should be of considerable interest to students and medical practitioners who would like to get a better understanding of modern "functional" thinking.